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APPLICANT: LEHTOLA, VELI-MATTI ET AL.
SERIAL NO.: 09/486,971 GROUP: 1615
FILED: APRIL 11, 2000 EXAMINER: R. BENNETT
FOR: PHARMACEUTICAL PREPARATION COMPRISING
CLODRONATE AS ACTIVE INGREDIENT AND SILICIFIED
MICROCRYSTALLINE CELLULOSE AS EXCIPIENT

DECLARATION SUBMITTED UNDER 37 C.F.R. § 1.132

Honorable Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

I, Pertti Rantala, of Littoinen, Finland, do hereby declare the following:

I am presently the Vice President and Head of Research and Development for Focus Inhalation Oy. I have attached a copy of my curriculum vitae to this Declaration.

I am one of the inventors of the above identified patent application. I am also one of the inventors of the US Patent No. 5,525,354 (Posti et al).

I have read and understand the subject matter of the Office Action of March 1, 2001.

The following comments are offered in support of the patentability of the instant invention.

Our aim in Posti et al was to improve bioavailability of clodronate. This was achieved by formulating the preparation so that clodronate passes the stomach region in unliberated form and is released from the preparation only when it reaches the lower digestive tract. In practice, this objective was reached by enteric coating the drug delivery form with a film that dissolves at a pH from 5 to 7.2. This also means that the site of release of the active agent is different. The tablets of the present invention release the active agent in the stomach, whereas the enteric-coated tablets of Posti et al release the active agent in the lower digestive tract.

In Posti et al, we did not aim at reducing the tablet size. The total weight of the tablets of Posti et al is over 1300 mg, typically about 1340 to 1370 mg (the tablet core weighs 1300 mg, see Example 1, and the enteric coating film constitutes typically about 3 to 5% by weight of the total weight of the preparation, see column 2, lines 25 to 27). The total weight of the tablets exemplified in the present application varies between 1170 and 1250 mg. The tablets of Posti et al. are therefore much larger than the tablets of the present invention.

Furthermore, the amount of clodronate in the tablets of Posti et al is 61.5% (see Example 1) whereas in the exemplified tablets of the present invention it is from 64 to 68%. The amount of auxiliary agents in Posti et al is 23% whereas in the tablets of the present invention it may be as low as 14.5% (see for example Ex. 5).

In Posti et al we were not interested in improving the powder flow of the composition. Lubricants were mentioned in Posti et al only among other conventional additives, such as carriers, diluents, fillers, disintegrating agents etc., which are known in the art. According to my experience, however, silicified microcrystalline cellulose provides clodronate preparations with better powder flow than any of the previously reported auxiliary agents.

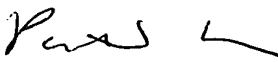
In the preparation process of Posti et al water is included in the mixture only at the stage where the clodronate granules are prepared. According to Posti et al, microcrystalline cellulose and silicon dioxide are added to dry clodronate granules. To my knowledge, it is therefore impossible that the teachings of Posti et al would lead to formation of silicified microcrystalline cellulose. As regards the Examiner's suggestion that wet granulation inherently produces silicified microcrystalline cellulose, I refer to the enclosed "Comparison of silicified microcrystalline cellulose (SMCC) and microcrystalline cellulose (MCC)" by Dr. Jouko Yliruusi. Dr. Yliruusi is Professor in Pharmaceutical Technology at the University of Helsinki and has carried out several

studies on the physical properties of silicified microcrystalline cellulose. As we knew that Dr. Yliruusi has expertise in the field of pharmaceutical excipients and has carried out several studies especially on silicified microcrystalline cellulose, we requested him to give an expert opinion on the physical properties of silicified microcrystalline cellulose and the blend containing microcrystalline cellulose and silicon dioxide.

To my experience, the use of silicified microcrystalline cellulose in clodronate preparations provides several advantages compared to the use of traditional microcrystalline cellulose and silicon dioxide. These advantages include i.a. better compactibility, tablet strength and powder flow, reduced friability, the possibility to use smaller amount of auxiliary agents and to increase the amount of the active agent in the preparation as well as to increase the production rate. The increase in crushing strength and the decrease in friability as well as the possibility to use higher tableting speeds are clearly shown in Example 8 of the above identified patent application.

The undersigned hereby declares that all statements made herein based upon knowledge are true, and that all statements made based upon information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Dated: 21. 6. 2001



Pertti Rantala

Enclosures:

As stated above

Pertti Rantala

June 7, 2001

CURRICULUM VITAE

| | |
|-------------------------|---|
| Name | <u>Pertti Rantala</u> |
| Date of Birth | March 3, 1943 |
| Nationality | Finnish |
| Education | M.Sc., University of Turku, 1971 Organic chemistry, mathematics, physics, statistics |
| Languages | Finnish, English |
| Current job description | Responsible for the research and development |
| Working experience | |
| 2000 - | Focus Inhalation Oy, Research and Development; Vice President, Research and Development |
| 1996 - 2000 | Leiras Oy, Research and Development; Head of Product Development for Therapeutics |
| 1992 - 1996 | Leiras Oy, Research and Development; Product Development Manager |
| 1989 - 1992 | Orion Oy Lääkefarmos, Research and Development; Laboratory Manager |
| 1985 - 1989 | Orion Oy Lääkefarmos, Research and Development; Project Manager |
| 1973 - 1985 | Lääke Oy, Quality Control; Laboratory Manager |
| 1972 - 1973 | Lääke Oy, Research and Development; Scientist |
| 1970 - 1972 | Neste Oy, Quality Control, Ethylene plant and power station; Supervisor |
| Additional education | |
| 2001 | Formulation Strategies for Biopharmaceuticals, San Diego, California, US, 2 d |
| 2001 | Non -traditional Approaches for Biotechnology Drug Delivery, San Diego, California, US, 1 d |
| 2000 | Achema 2000 Meeting, Frankfurt, DE, 6 d |
| 2000 | Effective Strategies for Conducting Failure Investigation, Washington, Washington D.C., US, 3 d |
| 2000 | Katalyytti, Jakso I - III |
| 1999 | AAPS Annual Meeting & Exposure, New Orleans, Louisiana, US, 5 d |

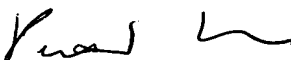
- 1999 Protein and Gene –based Drugs: Product Development and Delivery Challenges, New Orleans, Louisiana, US, 1 d
- 1999 Improving Drug Delivery from Pressurized Inhalation, London, GB, 2 d
- 1999 Regulatory Issues Related to Drug Products for Oral Inhalation and Nasal Delivery, Washington, Washington D.C., US, 2 d
- 1998 AAPS Annual Meeting & Exposure, San Francisco, California, US, 4 d
- 1998 Crystallization in the Pharmaceutical Sciences, San Francisco, California, US, 1 d
- 1998 Scale-up and Process Validation in Pharmaceutical Manufacturing, London, GB, 1 d
- 1998 Recent Advances in Dry Powder Inhalation, London, GB, 2 d
- 1997 AAPS Annual Meeting & Exposure, Boston, Massachusetts, US, 5 d
- 1997 Laatuseminaari, Tuusula, FI, 2 d
- 1997 Global Transfer of Production Sites, London, GB, 1 d
- 1997 Fysikaalisen Farmasian VIII Symposium, Kuopio, FI, 1 d
- 1996 New Horizon in Pulmonary Drug Delivery, London, GB, 2 d
- 1996 23rd Int. Symposium on CR of Bioactive Materials, Kyoto, JP, 2 d
- 1996 Development of Hydrogel Dosage Forum, Kyoto, JP, 2 d
- 1996 Recent Advances in Dry Powder Inhalation, London, GB, 2 d
- 1995 Biocompatibility Testing and Regulatory Issues, Workshop, Seattle, Washington, US, 2 d
- 1995 Post –Approval Changes for Sterile Aqueous Solution (PAC – SAS), Washington, Washington D.C., US
- 1995 22nd Int. Symposium on Controlled Research of Bioactive Materials, 4 d
- 1995 Patient Compliance Factors in Pharmaceutical Development, Workshop, Seattle, Washington, 1 d
- 1995 Laatuseminaari, Tuusula, 2 d
- 1994 Projektikokous, Projekti –instituutti PTY Oy, Leiraksen tiloissa, 1 d
- 1994 Leiraksen johtamistaidollinen valmennus /johto I, 1 d
- 1994 21st Int. Symposium of CR of Bioactive Materials, Nice, FR, 4 d
- 1994 Colon –Specific Drug Therapy, Workshop, Nice, FR, 2 d
- 1994 US Drugs Approval Process, London, GB, 2 d
- 1994 Controlled Release Society, Workshop of Regulatory Affairs, Washington, Washington D.C., US, 2 d
- 1994 Fysikaalisen farmasian V symposium, Orion Yhtymä Oy, Espoo, FI, 1 d
- 1993 20th Int. Symposium of Controlled Research of Bioactive Materials, Washington, Washington D.C., US, 6 d
- 1993 XII Helsinki University Course in Drug Research, Helsinki, FI, 2 d
- 1993 Laatuseminaari, Tampere, FI, 2 d

Pertti Rantala

June 7, 2001

- | | |
|------|---|
| 1993 | 4 th Int. Symposium on Disposition and Delivery of Peptide Drugs, Leiden, NL, 3 d |
| 1992 | Product Development: Correlation to Human Performance, Orlando Florida, US, 2 d |
| 1992 | 19 th Int. Symposium on Controlled Research of Bioactive Materials, Orlando Florida US, 6 d |
| 1990 | Packaging of Samples for Clinical Trials, Liverpool, GB, 3 d |
| 1984 | Conference on new trends in validation of drug manufacturing processes, Stockholm, SE, 3 d |
| 1980 | Validation of Manufacturing Processes, Geneva, CH, 2 d |

Signature





Comparison of silicified microcrystalline cellulose (SMCC) and microcrystalline cellulose (MCC)

Summary

Physical appearance of SMCC (silicified microcrystalline cellulose) and MCC (microcrystalline cellulose) are compared on the basis of scientific publications. It is concluded, that there are significant differences in the physical properties of SMCC and MCC and SMCC is not a simple physical mixture of MCC and silicon dioxide.

Introduction - materials structure

People often believe that (pharmaceutical) formulation is just mixing of different materials. This is not true. In drug product formulation numerous factors are influencing simultaneously. Examples of the factors are e.g. particle size or particle shape (distributions), mixing efficacy, moisture content of various components, mixing order (sometimes a certain component is added in several steps into the mixture), amounts mixed together, effect of equipment used etc.

In a way, also new advanced excipients can be considered as a result of formulation work.

Physical structure of a pharmaceutical solid excipient is not just a simple combination of excipient molecules, but rather higher level organised structures, which may contain oriented crystallites with specific crystal properties and self assembled molecules. This is the way that we understand different polymorphic forms or various microcrystalline states of materials.

Comparison of MCC and SMCC

Microcrystalline cellulose (MCC) is manufactured from dissolving pulp by acid hydrolysis. After washing with water the suspension is spray dried into microcrystalline powder. The manufacturing process shortens the cellulose chains and removes the dissolving cellulose fibres (hemicellulose and lignin). The degree of polymerisation in MCC is about 220, when that of powdered cellulose is about 1400. Powdered cellulose is a milling product of dissolving pulp. The degree of crystallinity is higher in MCC (65-75%) than in powdered cellulose (15-45%).

Silicified microcrystalline cellulose (SMCC) is produced by co-processing colloidal silicon dioxide together with MCC, i.e. silicon dioxide slurry is added to the MCC slurry before spray drying.

There are number of papers in which the physical properties of MCC and SMCC have been compared. However, only few papers have been published of the comparison of SMCC and physical blend containing MCC and silicon dioxide. In those very few cases the results have shown that SMCC and a physical dry blend of MCC and silicon dioxide are not equivalent.

In 2000 S.Edge et al. compared the compactibility of silicified materials (SMCC90 and SMCCHD90), unsilicified materials (MCC90, MCCHD90) and dry blend of silicon dioxide and MCC. They concluded that silicified materials exhibit greater compactibility than their respective unsilicified powders. The dry blend of MCC and silicon dioxide exhibits a decrease in compactibility compared to unmodified MCC.

In 2001 E. Lahdenpää et. have showed that there is a significant difference between Prosolv SMCC 90 and Avicel PH-102/Aerosil mixtures. The distribution of colloidal silicon dioxide in Prosolv SMCC 90 was found to be uniform. When simply mixed with Avicel PH-102, colloidal silicon dioxide was not distributed uniformly. The determinations were made by an energy dispersive x-ray spectroscopy, which was attached in a scanning electron microscope.

Conclusion

On the basis of my experience and the research made in my own research groups as well as on the basis of the well-known public research groups I do assure that there are significant differences between SMCC and MCC and SMCC is not a simple physical mixture of MCC and silicon dioxide.

Helsinki 28th of May 2001

Sincerely



Jouko Yliruusi
Professor in Pharmaceutical Technology
PhD (pharm.)
MSc (physics), MSc (pharm.)

Appendixes

1. References

- E. Lahdenpää, O. Antikainen and J. Yliruusi, Direct compression with silicified and non-silicified microcrystalline cellulose: study of some properties of powders and tablets, S.T.P. Pharma Sciences, 11 (2) 129-135, 2001.
- Bob E. Sherwood et al., Flow, Tableting & Compaction Characterization of High Density (HD) Silicified Microcrystalline Cellulose (SMCC), Conference Proceedings, Vol 3, pp.207-210, April 13th, 2000, 19th Pharmaceutical Technology Conference, Baveno-Stresa, Italy, 2000.
- G. Buckton et al., The use of NIR Spectroscopy to Study the Difference between Emcocel and Prosolv SMCC before and after Wet Granulation, Conference Proceedings, Vol 3, pp. 17-27, March 26th, 1998, 17th Pharmaceutical Technology Conference, Trinity College, Dublin, Ireland, 1998.
- S.Edge et al., Compactability of Microcrystalline Cellulose/Silicon Dioxide Composites, Conference Proceedings p.13-14, 46th Annual Congress of APV/APGI 9th International Conference on Pharmaceutical Technology, 3rd World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Berlin 3 to 6 April 2000.
- S.Edge et al., Physical and Mechanical Characterization of High Density (HD) Silicified Microcrystalline Cellulose,Conference Proceedings, pp. 61-62, 46th Annual Congress of APV/APGI 9th International Conference on Pharmaceutical Technology, 3rd World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Berlin 3 to 6 April 2000.
- B.E. Sherwood and J.W. Becker, A new class of high-functionality excipients: Silicified microcrystalline cellulose. Pharm. Technol., 10, 78-83, 1998.
- P. Luukkonen, T Schaefer, L Hellen, A.M. Juppo and J. Yliruusi, 1999, Rheological characterization of microcrystalline cellulose and silicified microcrystalline cellulose wet masses using a mixture torque rheometer, Int. J. Pharm., 188, 181-192.
- P. Luukkonen, T Schaefer, F. Podczek, J.M. Newton, L Hellen, A.M. and J. Yliruusi, 2001, Characterization of microcrystalline cellulose and silicified microcrystalline cellulose using a powder rheometer. Eur.J.Pharm.Sci. 13, 143-149.
- P. Luukkonen, T. Maloney, J. Rantanen, H. Paulapuro and J. Yliruusi, Microcrystalline cellulose-water interaction – a novel approach using thermoporosimetry. Submitted for publication.
- M.J. Tobyn et al., Physicochemical comparison between microcrystalline cellulose and silicified microcrystalline cellulose, Int. J. Pharm., 169, 183-194, 1998.

2. Short CV of the expert

1. Full name

Jouko Kalervo Yliruusi

2. Date and Place of Birth

26.10. 1952, Sumiainen, Suomi.

3. Current Position

Professor, Pharmaceutical Technology, Head of Department, University of Helsinki.

4. Education

| | |
|---------------|------|
| MSc (pharm.) | 1980 |
| Lis. (pharm.) | 1985 |
| MSc (physics) | 1986 |
| PhD (pharm.) | 1987 |
| Dos (pharm.) | 1990 |

5. Previous Positions

ORION PHARMA

| | |
|--|-------------|
| Scaling-up pharmacist | 1980 - 1982 |
| Group Leader (Development of Parenteral Products) | 1982 |
| Head of Scaling-up Group | 1983 - 1985 |
| Head of Laboratory (Pharmaceutical Process Laboratory) | 1985 - 1989 |
| Department Manager (Department of Physical Pharmacy) | 1989 - 1990 |

UNIVERSITY OF HELSINKI

| | |
|---|-------------|
| Assoc. prof. (Pharm. Technology) | 1990 - 1993 |
| Professor (Pharm. Technology), Head of Department | 1996 - |

6. External Funding

The total amount of external funding during 1990-2000 for my research is about 20 million FIM. Main supporters have been Tekes and Finish Pharmaceutical and Food Industry.

7. Publications

| | | |
|---|-------|-----|
| Original publications in journals with referees | about | 140 |
| Long abstracts in congress proceedings | over | 50 |
| Posters | about | 200 |

8. Membership in Scientific Organisations

AAPS, American Association in Pharmaceutical Sciences
Finnish Physical Pharmacy Association
Finnish Pharmaceutical Association

9. Other Academic Activities

| <u>ACTIVITY</u> | <u>AMOUNT</u> |
|------------------------------------|---------------|
| Referee of PhD Theses | 5 |
| Referee of Assistant Professorship | 1 |
| Supervisor of PhD Theses | 18 |
| Supervisor of MSc Theses | |
| - Pharmaceutical Technology | about 100 |
| - Physics | 1 |
| - Engineering | 5 |

Currently I have 19 active PhD students.

Honorary Visiting Professor in Pharmacy, University of Bradford 1992.

| | |
|--|-------------|
| Scientific advisor (Orion-Farmos) | 1990 - 1993 |
| Scientific advisor (Orion Pharma) | 1993 - 2000 |
| Member in the Board of Pharmacy tutkijakoulu | 1997 - |
| Head of NorFA Network on Pharmaceutical Technology and Biopharmaceutics | 1996 -1999 |
| Member of the Board in Viikki Drug Discovery Technology Center | 2000 - |
| Responsible Professor in Specialising Studies in Industrial Pharmacy | 1999 - |
| Member of the International Advisory Board (Pharmaceutical Technology Conference, Liverpool) | 2000- |
| Member in the Advisory Board (Helsinki Univ. Drug Research) | 1995 - |

A New Class of High-Functionality Excipients: Silicified Microcrystalline Cellulose

Bob E. Sherwood* and John W. Becker



Research directed toward reducing lost compaction functionality of microcrystalline cellulose (MCC) after wet granulation has led to the development of a new excipient known as silicified microcrystalline cellulose. This material exhibits improved compactibility in direct compression or after wet granulation, as well as better flow. This article discusses the enhanced functional benefits of the two commercial grades of this excipient, which is prepared by co-processing MCC with colloidal silicon dioxide.

Tablets and capsules are central to the pharmaceutical industry, and excipients play a key role in their formulation and manufacture. The introduction of microcrystalline cellulose (MCC) as a tablet binder in the 1960s was a major advancement for the production of many solid dosage formulations. MCC enabled formulators to develop effective direct-compression and wet granulation processes, to produce uniform particle properties, and to produce tablets with improved bioavailability.

Although MCC offers significant benefits compared with previous excipients, it does have limitations such as low bulk density, poor flow characteristics, loss of compactibility after wet granulation, and sensitivity to lubricants. Despite the subsequent introduction of alternative MCC grades such as high density, low moisture, and larger particle sizes — which singularly address some of the deficiencies — problems still exist in the use of MCC in formulation development. As a result of these limitations, improved ex-

cipients with greater functionality are still needed.

Some new chemical entities, including proteins, peptides, and actives derived from natural sources, demand greater excipient functionality. As manufacturing technology becomes more sophisticated — i.e., new manufacturing equipment and new formulation methods are used — and as development and process times and manufacturing efficiencies become more important, the need for better-performing excipients is inevitable.

Silicified microcrystalline cellulose (SMCC), a new, high-functionality pharmaceutical ingredient, was created to alleviate some of the known deficiencies of conventional MCC and to offer enhanced performance (1). The characteristics of this new material offer benefits in both direct-compression and wet granulation solid dosage formulation and manufacturing (2–4).

Two methods are commonly used to produce solid dosage forms: wet granulation and direct compression. Wet granu-

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*To whom all correspondence should be addressed.

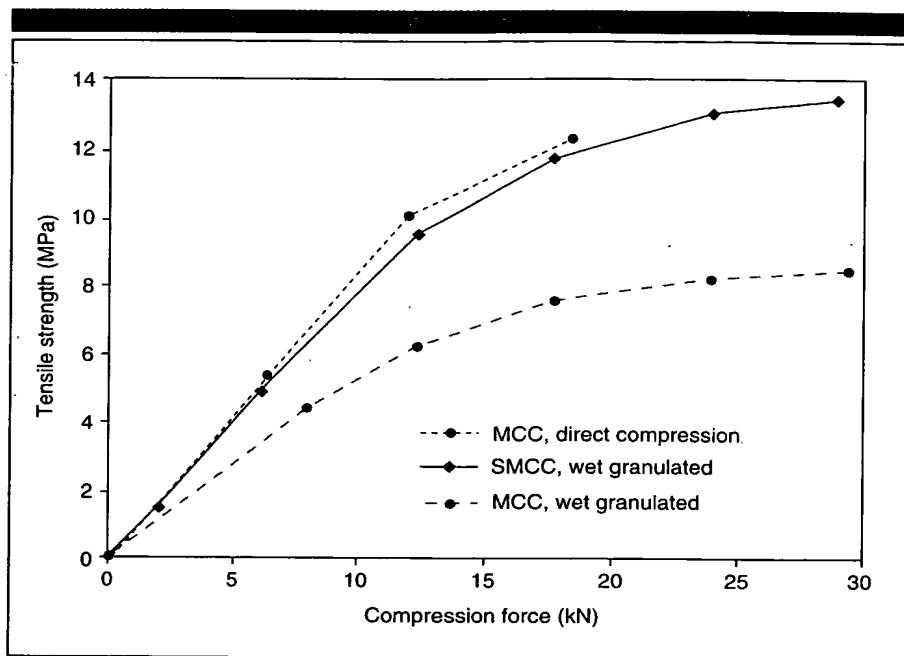


Figure 1: Effect of wet granulation on SMCC 50 and MCC.

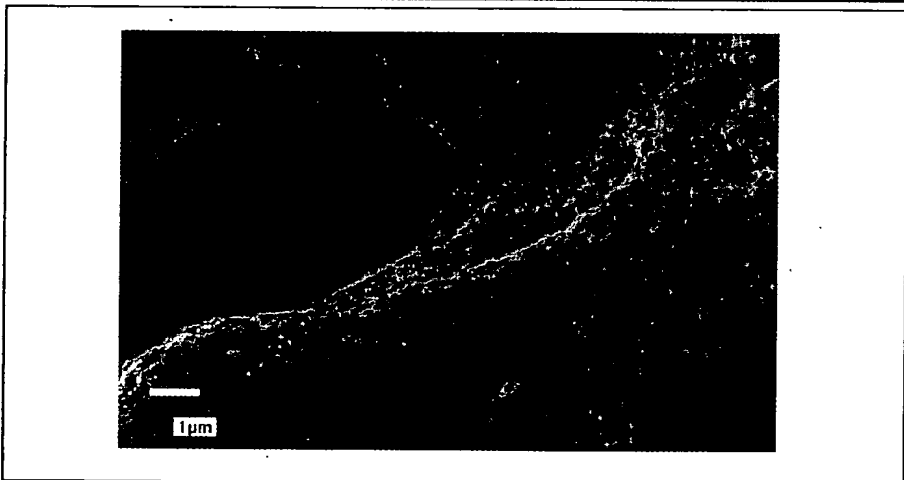


Figure 2: SMCC 90 scanning electron micrograph (10,000 \times magnification).

lation may be used to enhance formulation flow and compactibility by the addition of binders, and it may improve content uniformity in formulations with low active content. However, compared with direct compression, the benefits of wet granulation are at least partially offset by the need for capital investment in facilities and additional equipment, as well as being more labor and energy intensive. Furthermore, the introduction of heat and solvents can be detrimental to product stability. When MCC is used as a binder in wet granulation, compaction function-

ality is lost during the process, and the introduction of additional, extragranular MCC is generally required to achieve satisfactory tablet hardness.

Direct compression is a simpler and more economical manufacturing process than wet granulation. It requires less equipment, is less labor and energy intensive, and does not require the addition of solvents or heat. Because direct compression involves fewer processing steps, one might expect validation to be accomplished more easily. However, direct compression challenges excipients to be more

functional in providing adequate flow and sufficient compactibility for high unit dose drugs and in promoting content uniformity for low unit dose drugs.

Recognizing the loss in functionality of MCC when it is wet granulated with water (see Figure 1), researchers at the University of Bath and the Mendell division of Penwest Pharmaceuticals Company conducted studies to determine the cause. After studying a process that occurs in paper making, Professor John Staniforth of the University of Bath coined the term *quasi-hornification* to describe reduced bonding capacity following wetting and drying of cellulose fibers (2). The researchers concluded that the reduced bonding was the result of a high degree of lateral association, which is facilitated by wetting and promotes the formation of intra- and interfiber hydrogen bonds during drying. The tenacity of this hydrogen bonding reduces subsequent accessibility of water to cellulose fibers.

To overcome quasi-hornification, a product development effort investigated many potential approaches and led to a novel process for combining MCC and colloidal silicon dioxide (CSD). The patented product results from intimate association of CSD with MCC and is referred to as silicified microcrystalline cellulose (SMCC). The developers investigated the use of various amounts of MCC and CSD, and an effective combination of 98% MCC co-processed with 2% CSD was commercialized as PROSOLV SMCC (Mendell Division, Penwest Pharmaceuticals Co., Patterson, NY).

The excipient is available in the two particle-size grades most commonly used for MCC. SMCC 90 is a large-particle grade with a particle-size distribution equivalent to that of Emcocel 90M (Penwest Pharmaceuticals Co.) and Avicel PH-102 (FMC Corp., Philadelphia, PA). This grade is recommended primarily for use in direct compression. SMCC 50 has a particle-size distribution similar to that of Emcocel 50M and Avicel PH-101. This grade is recommended especially for wet granulation. It can also be used effectively in direct-compression formulations, either alone or in combination with SMCC 90, to minimize segregation.

Scanning electron microscope studies (see Figure 2) have demonstrated that intimate physical association of CSD with

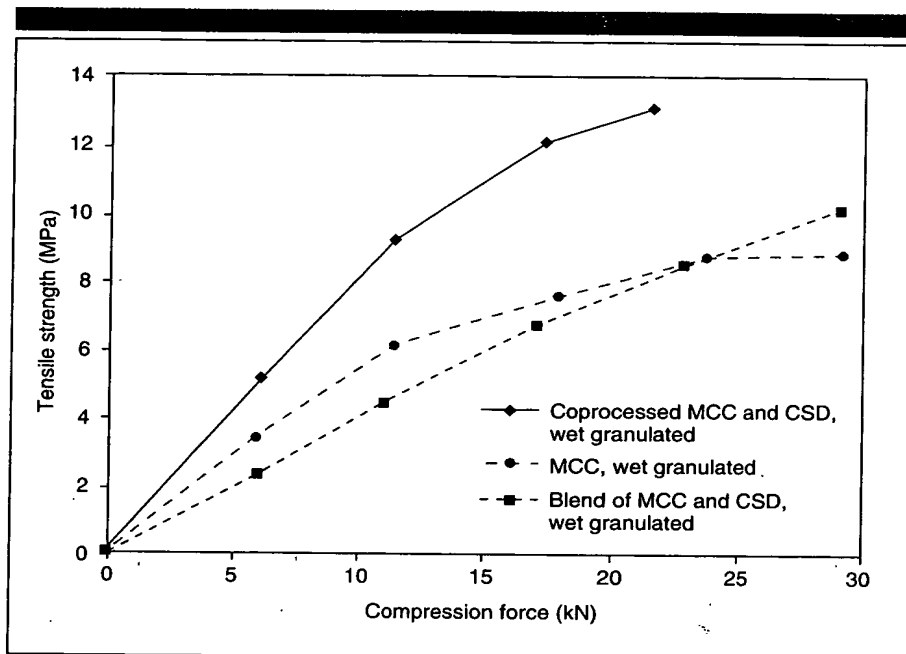


Figure 3: Effect of co-processing MCC and CSD on wet granulation performance.

Table I: Effect of wet granulation on density.

| | Ungranulated Density (g/cm ³) | Granulated Density (g/cm ³) | Percent Change |
|---------------------------|---|---|----------------|
| Commercial MCC (grade 50) | 0.30 | 0.51 | +70% |
| SMCC 50 | 0.33 | 0.36 | +9% |

the cellulose particles occurs on the surface and within the particles (5). Other studies using mercury porosimetry, gas adsorption, and X-ray dispersion analysis (6); solid-state NMR, IR spectroscopy, and X-ray diffraction evaluation of crystallinity (7); calorimetry and water vapor sorption (8); and Raman spectroscopy (9) have detected no chemical changes and indicate similarity to MCC's physicochemical properties.

WET GRANULATION PERFORMANCE

A standardized test was used to develop SMCC and to improve its compactibility after wet granulation. In comparative studies, SMCC and MCC were granulated in the same manner using a high-shear, 10-L Baker-Perkins mixer-granulator (B&P Process Equipment and Systems, Saginaw, MI) for 3 min, using water equivalent to 42% of the wet mass as the granulating fluid. This amount of water has been shown to result in maximum loss

of compaction of MCC (10). The wet mass was screened through a 12-mesh screen and tray-dried for ~3 h to a moisture content of ~5%.

To eliminate granulate particle-size distribution as a variable in assessing compactibility, granulations were sieved and reconstituted into a standardized mixture of particles in the range of 74–177 μm . These particles were blended with 0.25% sodium stearyl fumarate (Pruv, Penwest Pharmaceuticals Co.) in a twin-shell blender. Tablets (round, flat-face, $\frac{1}{8}$ -in. diameter, 250 ± 5 mg) were compacted over a force range of 2–30 kN using a Korsch PH106 instrumented tablet press (Korsch America, Somerset, NJ). The hardness, thickness, and diameter of at least 10 tablets were measured using an Erweka TBH30 tester (Erweka USA Inc., Milford, CT). Tensile strengths, calculated from these measurements by the method of Newton and Fell (11), are reported as mean values.

The results of wet granulation functionality studies demonstrate that SMCC produces harder tablets compared with MCC (see Figure 1). Tablets with a tensile strength of ~5 MPa were produced from granulated SMCC at a compaction force of only 6 kN. By comparison, MCC tablets produced at equivalent compaction force were found to have a 40% lower tensile strength. Furthermore, the compactibility of SMCC following granulation continued to rise steeply with increasing compaction force, up to the limit of the hardness tester, in a profile similar to that for ungranulated MCC (direct compression).

Additional studies have shown that co-processing of CSD with MCC to achieve an intimate association is necessary to derive the beneficial functionality. Figure 3 shows the effects of wet granulating MCC alone; CSD co-processed with MCC (SMCC); and an equivalent, simple blend of CSD and MCC. This figure demonstrates that SMCC compacts better than wet granulated commercial MCC or a blend of MCC and CSD.

Table I illustrates a notable observation: SMCC does not exhibit the same level of densification (loss of porosity) upon wet granulation as does MCC (2). The grade of MCC normally used in wet granulation was found to densify by ~70% upon granulation, whereas SMCC granulation densified by <10%. Densification is related to the loss of compactibility.

DIRECT-COMPRESSION PERFORMANCE

In addition to providing benefits in wet granulation applications, SMCC demonstrates enhanced functionality in direct-compression processes. Several physical and functional properties of SMCC have been found to be beneficial in direct compression. These benefits include enhancement of direct-compression compactibility, significant improvement in material flow, and reduction in lubricant sensitivity.

Direct-compression studies involved dry blending the ingredients with 0.25% Pruv lubricant in a twin-shell blender for 3 min, followed by compaction on a Korsch PH106 instrumented tablet press, as described in the wet granulation studies.

SMCC is the most compactible substance known to date to be acceptable for pharmaceutical applications (12).

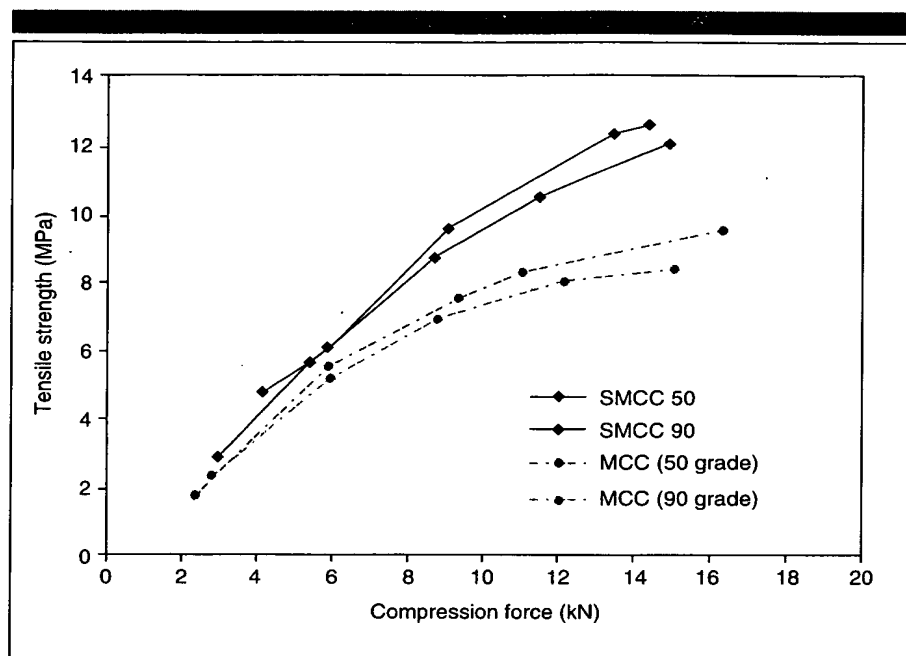


Figure 4: Direct compression of SMCC and MCC.

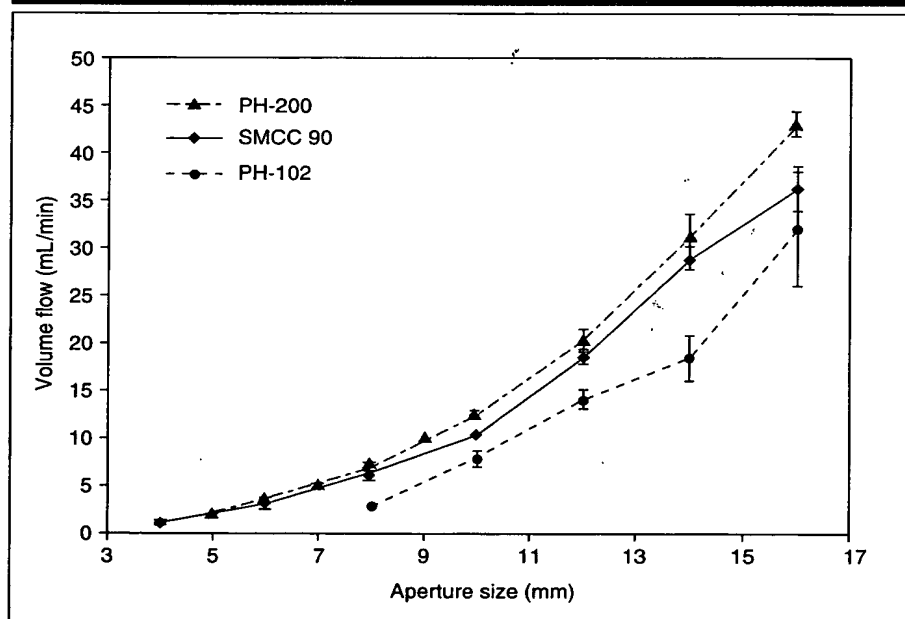


Figure 5: Comparison of volume flow.

Figure 4 shows that in direct compression, SMCC is ~10–40% more compactible than regular MCC. Co-processing of CSD with MCC is essential for the enhanced compactibility in both direct compression and wet granulation.

Studies presented so far in this article represent placebo tablets; some actual commercial formulations have demon-

strated 50–70% more compactibility with SMCC than with MCC. With SMCC, poorly compactible actives, even in high concentrations, can now be accommodated in direct-compression processes.

FLOW CHARACTERISTICS

The improved flow characteristics of SMCC compared with MCC can improve

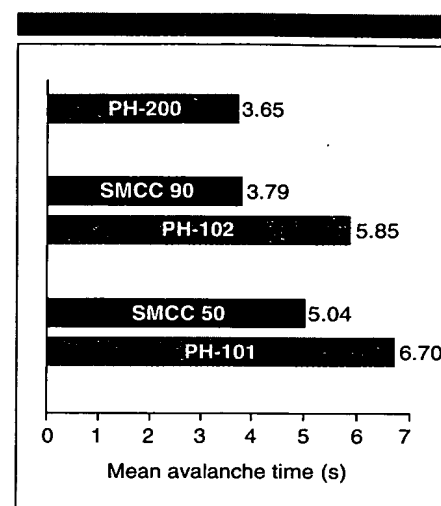


Figure 6: Comparison of dynamic material flow.

tablet weight uniformity and drug content uniformity in direct-compression solid dosage manufacturing (see Figures 5 and 6). Flow measurements in Figure 5 were obtained using a Hanson Flodex apparatus (Hanson Research Corp., Chatsworth, CA). Flow time of a mass of powder through a series of decreasing aperture sizes was determined until bridging prevented flow or until the minimum available (4 mm) aperture was reached. Mass flow rate was determined and converted to volume flow rate using the bulk density of each material.

A comparison of SMCC 90 and PH-102 MCC, which have similar particle sizes and densities, demonstrates the superior flow of SMCC. PH-102 bridged over apertures smaller than 8 mm, while SMCC 90 flowed through apertures as small as 4 mm. The flow rates for SMCC 90 were equivalent to those of the larger particle-size PH-200 grade of MCC.

Avalanching flow properties further demonstrate the superiority of SMCC flow under dynamic conditions. These studies used 60 mL of powder sample in an AeroFlow analyzer (Amherst Process Instruments, Amherst, MA) rotating at 0.33 rpm. The apparatus measures the time between avalanches as test material is lifted in a rotating drum. Figure 6 shows the results for both grades of SMCC and comparable grades of MCC. The more frequent and better flow of both SMCC grades compared with similar particle-size grades of MCC is particularly evident in the figure.

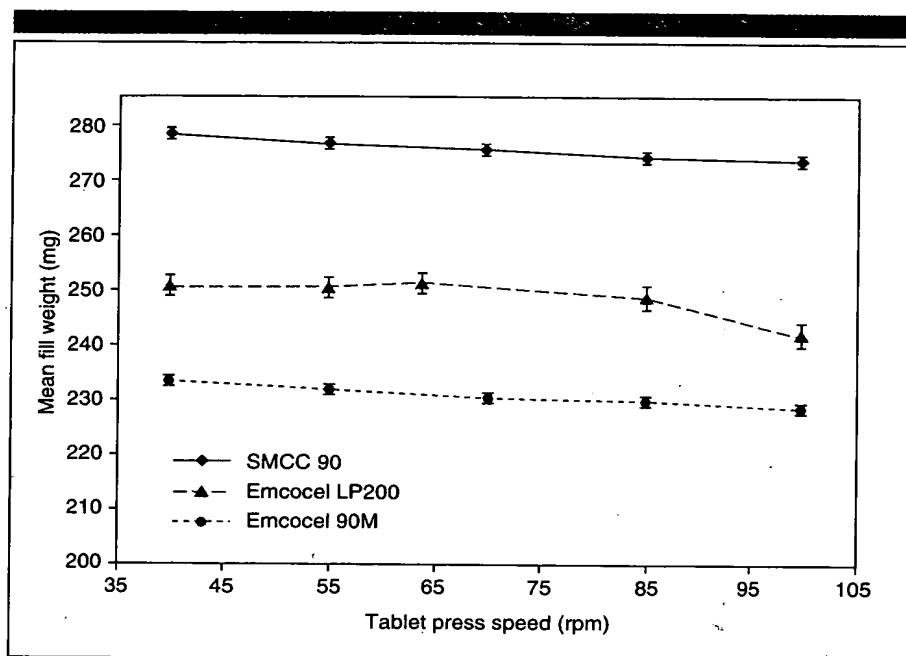


Figure 7: Effect of press speed on comparative fill weight and weight variation.

Table II: Tablet weight variation as a function of press speed.

| Press Speed (rpm) | Emcocel 90M | | SMCC 90 | | Emcocel LP200 | |
|----------------------|-------------|---------|-----------|---------|---------------|---------|
| | Mean (mg) | RSD (%) | Mean (mg) | RSD (%) | Mean (mg) | RSD (%) |
| 40 | 233 | 0.36 | 278 | 0.38 | 251 | 0.61 |
| 55 | 232 | 0.34 | 277 | 0.37 | 251 | 0.59 |
| 70 | 230 | 0.37 | 276 | 0.39 | 251 | 0.55 |
| 85 | 230 | 0.42 | 274 | 0.38 | 249 | 0.73 |
| 100 | 229 | 0.56 | 274 | 0.43 | 242 | 0.94 |

Table III: Calculated percent of initial compressibility as function of 0.5% magnesium stearate blend time.

| Compaction Force (kN) | PH-102 | | | SMCC 90 | | |
|--------------------------|--------|------------|------------|---------|-------|--------|
| | 0 min | 5 min | 10 min | 0 min | 5 min | 10 min |
| 2 | 100% | 34% | 25% | 100% | 66% | 48% |
| 4 | 100% | 36% | 26% | 100% | 67% | 49% |
| 6 | 100% | 34% | 21% | 100% | 65% | 48% |
| 8 | 100% | 30% | 18% | 100% | 62% | 45% |
| 10 | 100% | 26% | 15% | 100% | 58% | 43% |
| 12 | 100% | 21% | 12% | 100% | 54% | 39% |
| 14 | 100% | Lamination | Lamination | 100%* | 49%* | 35%* |

*Projected because control > 14 MPa was too high to measure.

The enhanced flow properties of SMCC lead to excellent tablet weight uniformity when the material is applied in high-speed tableting operations (see Table II). In a trial using a 16-station Manesty Betapres (Thomas Engineering, Hoffman Estates, IL) with gravity feed, 1/8-in. round tablets

were produced from celluloses lubricated with 0.25% Pruv at speeds of 40–100 rpm (equivalent to approximately 38,000 to 97,000 tablets/h). No change was made in the fill adjustment between materials. Two hundred tablets from each speed were weighed on an analytical balance.

At fixed fill, each of the materials showed a slight decrease in mean weight as speed increased, which might be expected and easily corrected during tableting operations. More important, the relative standard deviations, indicative of the inherent flow properties of the materials, were all <1%. SMCC 90 showed a slight increase in RSD only at the highest speed; this increase was much smaller and occurred at a higher speed than was the case for the other materials tested, including the 200 particle-size grade of MCC, which is primarily designed for flow. The tablet weight data, presented graphically in Figure 7, demonstrate that greater packing density can be achieved with SMCC 90 due to its ease of flow and consolidation.

SMCC AND LUBRICANTS

A problem associated with many pharmaceutical ingredients is sensitivity to lubricants. The workhorse lubricant in pharmaceutical solid dosage forms, magnesium stearate, often causes a decrease in compactibility and may interfere with tablet disintegration and drug dissolution. SMCC demonstrates significantly less sensitivity to the compactibility-reducing effect of magnesium stearate (see Figure 8). Tablets were compressed with no lubrication (control equivalent to zero blend time) and after blending for 5 and 10 min with 0.5% magnesium stearate in a twin-shell blender. To eliminate experimental variation in average compression forces and to afford quantitative comparison, the data were fitted by second-order regression and the resulting equations were used to calculate the percent of compactibility retained (see Table III). Compared with PH-102 grade MCC, SMCC retained ~2–3 times the compactibility. Further, MCC tablets delaminated out of the press at compression forces >12 kN. Reduced lubricant sensitivity should prove beneficial in formulation robustness and ease of scale-up.

PROCESS CONVENIENCE

A number of the properties of SMCC described for wet granulation and direct compression lead to convenience in use. Another beneficial characteristic of SMCC is the fact that the CSD included in this product does not exhibit the fugi-

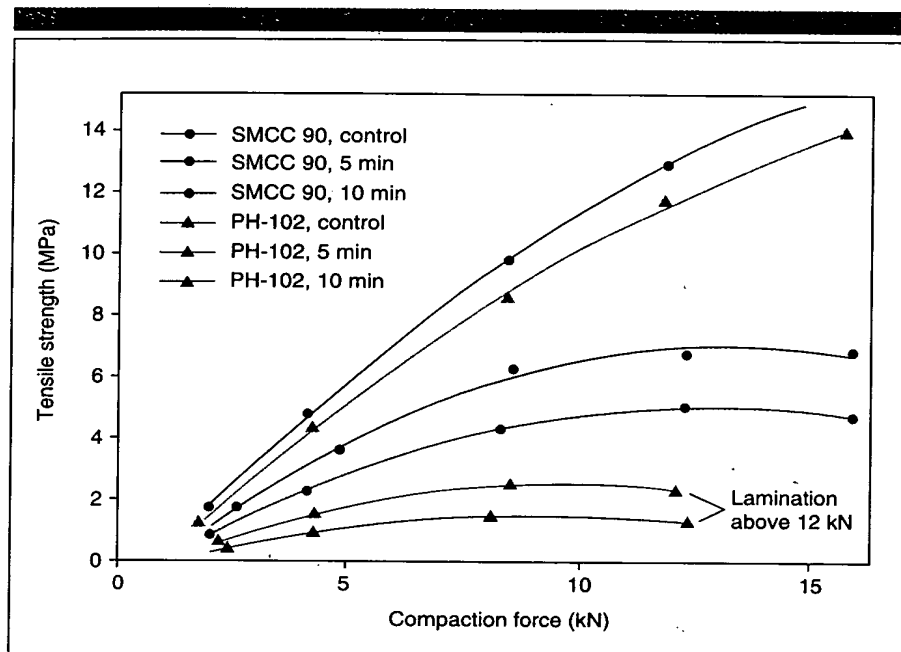


Figure 8: Effect of magnesium stearate (0.5%) blend time on compaction.

tive dusting associated with CSD (fumed silica). Consequently, SMCC can be used to introduce glidant properties, potentially eliminating or reducing the need for and the difficulties of handling CSD on a large scale. Substitution of SMCC in existing formulations that contain CSD is straightforward. FDA's SUPAC guidelines are instructive for determining the level of regulatory approval for this change in an existing formulation and manufacturing process.

CONCLUSION

For tablet or capsule formulation and manufacturing process improvements, the characteristics of SMCC provide significant advantages in both direct compression and wet granulation. SMCC can be used to overcome many formulation and manufacturing limitations.

Some characteristics of SMCC that may translate into formulation and pro-

cessing improvements for effectiveness, efficiency, and cost reduction include:

- improved direct-compression compactibility
- preservation of compactibility in wet granulation
- enhanced material flow properties
- reduced lubricant sensitivity
- nondusting (an alternative to fine powder glidants).

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Rheological characterization of microcrystalline cellulose and silicified microcrystalline cellulose wet masses using a mixer torque rheometer

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Abstract

The rheological properties of silicified microcrystalline cellulose (Prosolv 50) were compared with those of standard grades of microcrystalline cellulose (Emcocel 50 and Avicel PH 101). Cellulose samples were analyzed using nitrogen adsorption together with particle size, flowability, density and swelling volume studies. The rheological behaviour of the wet powder masses was studied as a function of mixing time using a mixer torque rheometer (MTR). Silicified microcrystalline cellulose exhibited improved flow characteristics and increased specific surface area compared to standard microcrystalline cellulose grades. Although the silicification process affected the swelling properties and, furthermore, the mixing kinetics of microcrystalline cellulose, the source of the microcrystalline cellulose had a stronger influence than silicification on the liquid requirement at peak torque. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Mixer torque rheometer; Microcrystalline cellulose; Silicified microcrystalline cellulose; Mixing kinetics

1. Introduction

Silicified microcrystalline cellulose (SMCC) is a combination of co-processed microcrystalline cellulose (MCC) and colloidal silicon dioxide. Edge

et al. (1998) found that silicon dioxide is primarily located on the surface of SMCC, and in some cases, silicon dioxide was also detected in the internal regions of some particles. Silicified microcrystalline cellulose provides better compactability and material flow properties than regular microcrystalline cellulose (Sherwood et al., 1996). SMCC has also been claimed to be more resistant

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to wet granulation than conventional MCC grades, since SMCC maintains compaction properties after wetting and drying. Staniforth and Chatrath (1996) suggested that the reduced bonding capacity of MCC was the result of the reversible formation of intra- and interfiber hydrogen bonds. Buckton et al. (1998) found in a NIR spectroscopy study that MCC, SMCC and wet granulated SMCC had essentially identical spectra, so there was no fundamental difference in the physical form of the cellulose in MCC and SMCC. Wet granulated MCC, on the other hand, showed differences indicating a minor change in internal hydrogen bonding. Tobyn et al. (1998) compared the physicochemical properties of MCC and SMCC using several different methods. They concluded that the silicification process produces a material which is chemically and physically very similar to standard MCC.

Several authors have studied the differences between regular microcrystalline cellulose grades, Avicel PH 101 and Emcocel (Staniforth et al., 1988; Raines, 1990; Newton et al., 1992; Landín et al., 1993a,b; Kleinebudde, 1997). A major cause of intermanufacturer variability among microcrystalline celluloses are the variability of the source of pulp and of the manufacturing process (Landín et al., 1993a,b). Penwest Pharmaceuticals changed the manufacturer and the source of pulp of the microcrystalline cellulose in 1990 (personal communication), so most of these previous studies were conducted with an Emcocel grade which is not equivalent to the currently used Emcocel 50.

It has been shown that the rheological properties of wet masses can be successfully monitored by a mixer torque rheometer (Parker et al., 1990; Rowe and Parker, 1994; Chatlapalli and Rohera, 1998). Several authors have compared the rheological properties of different MCC grades (Rowe and Sadeghnejad, 1987; Parker and Rowe, 1991; Hancock et al., 1992), but the rheological properties of silicified microcrystalline cellulose have not been studied previously. The amount of water added at the maximum torque should be comparable with that found for the optimum production of pellets during spheronisation (Miyake et al., 1973; Rowe and Sadeghnejad, 1987). In extrusion–spheronisation experiments with water-solu-

ble excipients the window of critical liquid requirement was slightly higher for the SMCC grade than for the MCC grade (Luukkonen et al., 1998).

The aim of this study was to investigate the rheological properties of silicified microcrystalline cellulose wet masses in comparison to the standard grades of MCC using a mixer torque rheometer and to correlate these with the physical properties of the materials.

2. Materials and methods

2.1. Materials

Microcrystalline cellulose (MCC) was obtained from two sources, Avicel PH 101 (6616C) from FMC (Co. Cork, Ireland) and Emcocel 50 (5S7547) and silicified microcrystalline cellulose (SMCC) Prosolv 50 (K5S6005) from Penwest Pharmaceuticals (Nastola, Finland). Silicified microcrystalline cellulose has a 2% w/w silicon dioxide concentration.

2.2. Particle size

The particle size distribution was studied using a Malvern 2600c (Malvern Instruments, England) equipped with dry powder feeder. The mean and median particle size data are the mean of three determinations.

2.3. Specific surface area

The specific surface area of each sample was determined in a Coulter SA 3100 apparatus (Coulter, Miami, FL). The samples were first degassed under vacuum at 40°C for 24 h. The pore volume size distributions were calculated from the nitrogen adsorption isotherms by the BJH model (Barrett et al., 1951). The specific surface area was tested in triplicate.

2.4. Flowability

The flowability was determined by an automatic flowability recorder (constructed at Orion

Corporation, Finland, i.e. non-commercial equipment). The angle of repose was determined by measuring the angle of the powder pile. Flowability was tested from six powder samples and the data were analyzed with the *t*-test.

2.5. Density

The poured and tapped densities of the materials were determined according to test of apparent volume (Ph. Eur. 2nd Ed.). True density measurements were made using a helium pycnometer (type Accupyc 1330, Micromeritics, Dunstable, UK). The density values are the mean of three determinations.

2.6. Swelling volume

The swelling volume was determined using a method described by Podczec and Révész (1993). 500 ± 0.5 mg of each material were placed in a 20 ml graduated test tubes with 10.0 ml of distilled water. The solids were suspended by vigorous shaking and allowed to settle down until the volume was constant. The swelling volume was noted and the relative increase on swelling calculated on the basis of the poured bulk volume. The experiments were carried out in triplicate.

2.7. Wet massing studies

The rheological profiles of the wet masses were monitored using a mixer torque rheometer (Model MTR, Caleva, Dorset, England) similar to that described by Parker et al. (1990) and Rowe (1995). Fifteen grams of dry powder was mixed in the rheometer for 3 min to obtain the baseline response. Water ($0.8\text{--}1.5$ ml g⁻¹) was

added in a single addition and the mixture was wet massed at 52 rpm for 12 min. The mixer torque rheometer measured two different torque parameters, the amplitude of the oscillations (torque range) and the mean torque increase from the baseline (mean torque). The mean torque describes the mean resistance of the mass to mixing and the torque range reflects the rheological heterogeneity of the mass. The mean torque was chosen since the torque range showed the same effects as the mean torque. All the wet massing experiments were performed in triplicate and a mean torque value and a standard deviation were calculated. The baseline response was deducted from torque responses. Curve fittings (three parameter log normal) were made by SigmaPlot 4.0 to the figures in which the mean torque values are as a function of mixing time.

3. Results and discussion

3.1. Particle size

The results of the particle size analysis are summarized in Table 1. There was no significant difference between cellulose samples.

3.2. Specific surface area and pore size distribution

The specific surface area data for the three celluloses are presented in Table 2. The surface area of Emcocel was slightly greater than that of Avicel, but the specific surface area of SMCC was about five times greater than that of regular microcrystalline cellulose. This is consistent with Staniforth et al. (1997). The results obtained for

Table 1
Particle size distribution^a

| | Mean diameter (μm) | <i>D</i> (<i>v</i> , 0.1) | <i>D</i> (<i>v</i> , 0.5) | <i>D</i> (<i>v</i> , 0.9) |
|---------------|--------------------|----------------------------|----------------------------|----------------------------|
| Avicel PH 101 | 59.7 ± 0.5 | 25.3 ± 0.1 | 60.2 ± 1.0 | 93.6 ± 0.4 |
| Emcocel 50 | 59.6 ± 0.2 | 25.1 ± 0.7 | 59.9 ± 0.2 | 93.5 ± 0.2 |
| Prosolv 50 | 58.6 ± 0.3 | 24.0 ± 0.7 | 58.8 ± 0.6 | 93.1 ± 0.2 |

^a *D* (*v*, 0.1) = 10 percentile, *D* (*v*, 0.5) = 50 percentile and *D* (*v*, 0.9) = 90 percentile of the particles.

Table 2
Specific surface area and pore volume of cellulose samples

| | BET surface area (m ² g ⁻¹) | Angle of repose (°) |
|---------------|---|------------------------|
| Avicel PH 101 | 1.14 ± 0.04 | 39.3 ± 1.3 |
| Emcocel 50 | 1.33 ± 0.01 | 38.6 ± 2.3 |
| Prosolv 50 | 6.34 ± 0.10 | 33.2 ± 1.3 |

Avicel PH 101 agree as well with those reported in the literature (Hancock et al., 1992; Landín et al., 1993a). The specific surface area of Emcocel is greater than in earlier studies by Landín et al. (1993a,b). This could be partly explained by the change in the source of wood pulp.

The pore volume size distributions calculated from the nitrogen adsorption isotherms showed that the total pore volume was quite similar between Avicel PH 101 and Emcocel 50 but much greater for Prosolv 50 (Fig. 1). The pore volume size distributions explain also the greater specific area of Prosolv 50. Edge et al. (1998) and Tobyn et al. (1998) found that silicon dioxide particles cause an extensive surface texturisation of SMCC. Colloidal silicon dioxide has a very large specific surface area and the differences in specific surface

area as well as in the pore distribution are ascribed primarily to the silicon dioxide on the surface of the SMCC.

Tobyn et al. (1998) determined pore size distributions for MCC 90 and SMCC 90 using a mercury porosimeter. They found the pore size characteristics to be very similar for MCC 90 and SMCC 90, and explained this by the similarity in envelope surface. Their method detected pores larger than 28 nm in diameter. In this study, however, the main difference in pore size distribution between MCC and SMCC is seen in the smaller pores.

3.3. Flowability and density

The flowability and density data can be seen in Tables 2 and 3. Prosolv showed better flowability than Avicel and Emcocel ($P < 0.0001$). SMCC showed also greater bulk and tapped densities than the regular MCC grades which is probably due to improved flowing and packing characteristics. These findings agree with those reported by Sherwood et al. (1996). The MCC grades had very similar flowability and density values.

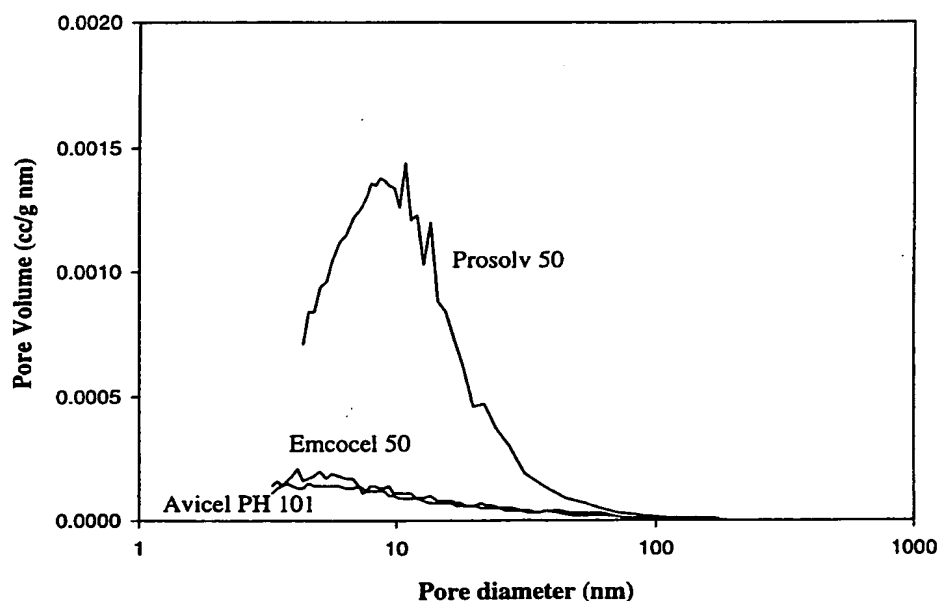


Fig. 1. Pore volume size distributions measured by nitrogen adsorption.

Table 3
Density and swelling volume measurements

| | Poured/tapped density (g cm ⁻³) | True density (g cm ⁻³) | Swelling volume (ml g ⁻¹) | Relative increase on swelling (%) |
|---------------|--|---------------------------------------|--|--------------------------------------|
| Avicel PH 101 | 0.31/0.42 | 1.54 | 4.8 ± 0.2 | 48.6 |
| Emcocel 50 | 0.31/0.41 | 1.54 | 4.7 ± 0.1 | 45.5 |
| Prosolv 50 | 0.35/0.47 | 1.55 | 4.3 ± 0.1 | 50.3 |

3.4. Swelling volume

Table 3 includes the swelling volume of the powder samples in water. The swelling volume was larger for MCC grades than for SMCC grade. However, the poured bulk volume of SMCC grade (2.86 ml g⁻¹) is smaller than the bulk volume of MCC grades (3.23 ml g⁻¹), so the relative increase on swelling was larger for SMCC grade. The difference between Emcocel and Prosolv was 4.8%. Podczek and Révész (1993) have previously reported that the relative increase on swelling varied from 27 to 44% between different microcrystalline cellulose grades.

3.5. Wet massing

All the material exhibited an increase in torque with increasing water content rising to a maximum, thereafter decreasing as the material became overwetted (Fig. 2). It has been suggested (Alleva, 1984; Rowe and Sadeghnejad, 1987) that this behaviour is consistent with the different states of liquid saturation (pendular, funicular and capillar) as defined by Newitt and Conway-Jones (1958). The transition between different states of liquid saturation is usually induced by increasing the level of binder liquid but an identical effect can be obtained also by consolidating the agglomerates by further mixing (Newitt and Conway-Jones, 1958; Kristensen and Schæfer, 1987).

3.5.1. Peak torque location

When a binder liquid is added to a solid material, it is gradually distributed throughout the powder bed by the mixing process. With increasing liquid content the number and extent of the

liquid bridges increases and a funicular state is formed. A further addition of liquid fills all the interparticulate voids, and the torque reaches a peak (capillary state). Prolonged mixing is assumed to cause a densification of the mass, and this should increase the liquid saturation causing a peak torque at a lower liquid amount. However, prolonged mixing will cause an increased absorption of water giving rise to a lower liquid saturation causing a peak torque at a higher liquid amount. The effect of mixing time on the peak torque location can be seen in Fig. 2a–d. With a shorter mixing time, the peak torque was achieved with a lower amount of liquid. With Emcocel, for instance, the peak torque location shifts during mixing from 1.1 ml g⁻¹ (Fig. 2b) to 1.3 ml g⁻¹ (Fig. 2d). The effect of absorption seemed to be larger than the effect of densification since a higher peak torque location was seen at prolonged mixing.

The mean torque profiles of MCC grades were quite similar after 1 min of mixing (Fig. 2a). When mixing time was increased to 3.5 min, the mean torque profile of Avicel was very close to the profile of SMCC grade (Fig. 2b). Further increase in mixing time decreased the difference between Emcocel and Prosolv and distinguished them from Avicel (Fig. 2c–d). In general, the mean torque values were smaller and the liquid requirement at peak torque was higher for Avicel (1.4 ml g⁻¹) than for Emcocel or Prosolv (1.3 ml g⁻¹). According to Ek and Newton (1998), variations in the performance of different sources of MCC is associated with the different interactions between the particular grade of MCC and water due to different pore structures. Staniforth et al. (1988) used a sandwich rheometer to measure the cohesiveness of microcrystalline celluloses. In

their study Avicel PH 101 was found to be more cohesive than Emcocel. Rowe and Sadeghnejad (1987) reported as well both higher torques and higher water contents for Avicel than for Emcocel. However, these studies were conducted with Emcocel grades which are not equivalent to the currently used Emcocel 50.

3.5.2. Mixing kinetics

The correlation coefficients of curve fittings varied between 0.999 and 0.968 for Avicel PH 101, 0.998 and 0.987 for Emcocel 50 and 0.999 and 0.987 for Prosolv 50. The typical relative

standard deviations of mean torques were less than 10%, with the exception of the lowest liquid level (0.8 ml g^{-1}) which showed much higher variations. At low liquid amounts ($0.8\text{--}1.2 \text{ ml g}^{-1}$), all the mean torque curves were descending after 4 min of mixing (Figs. 3a, 4a and 5a). At the lowest liquid amount the initial torque peaks were higher for the MCC grades (Figs. 3a and 4a) than for the SMCC grade (Fig. 5a). Alleva (1984) observed an initial force peak at low to intermediate liquid contents and attributed this to the uneven distribution of the granulating liquid and the formation of large unstable agglomerates.

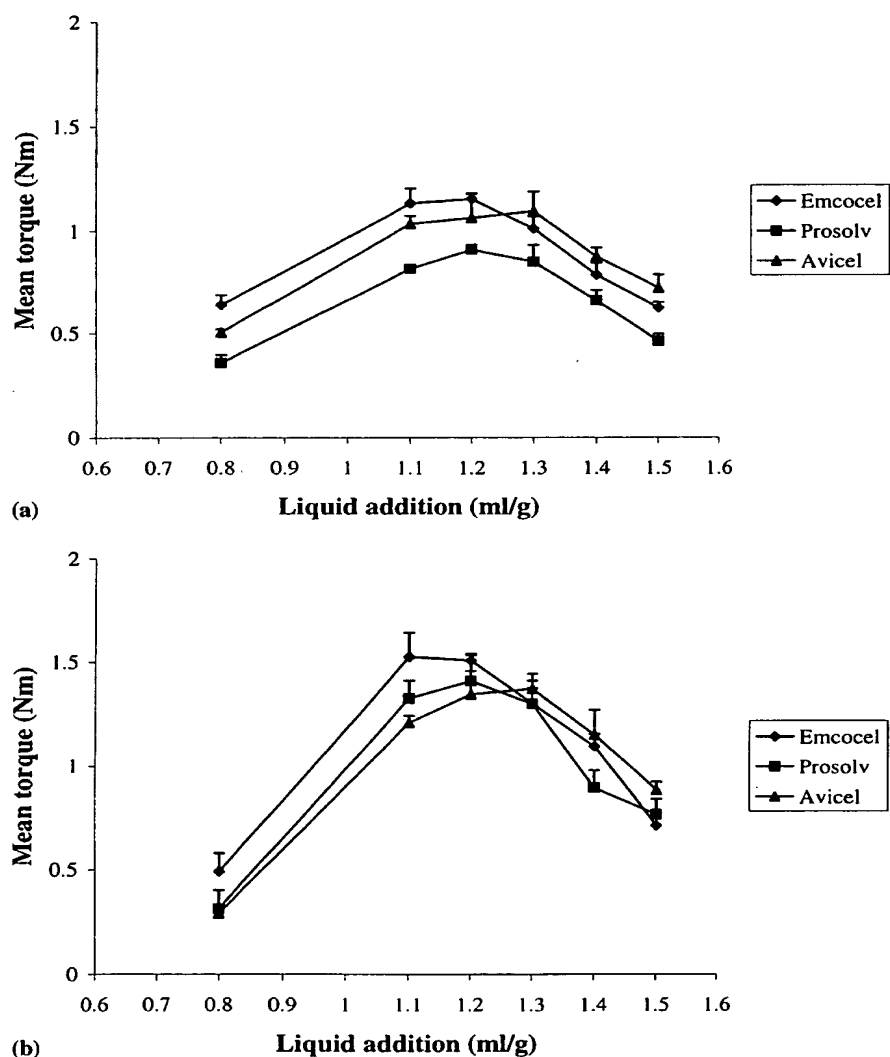


Fig. 2. Effect of mixing time on mean torque profile (a) 1 min (b) 3.5 min (c) 6 min (d) 12.25 min.

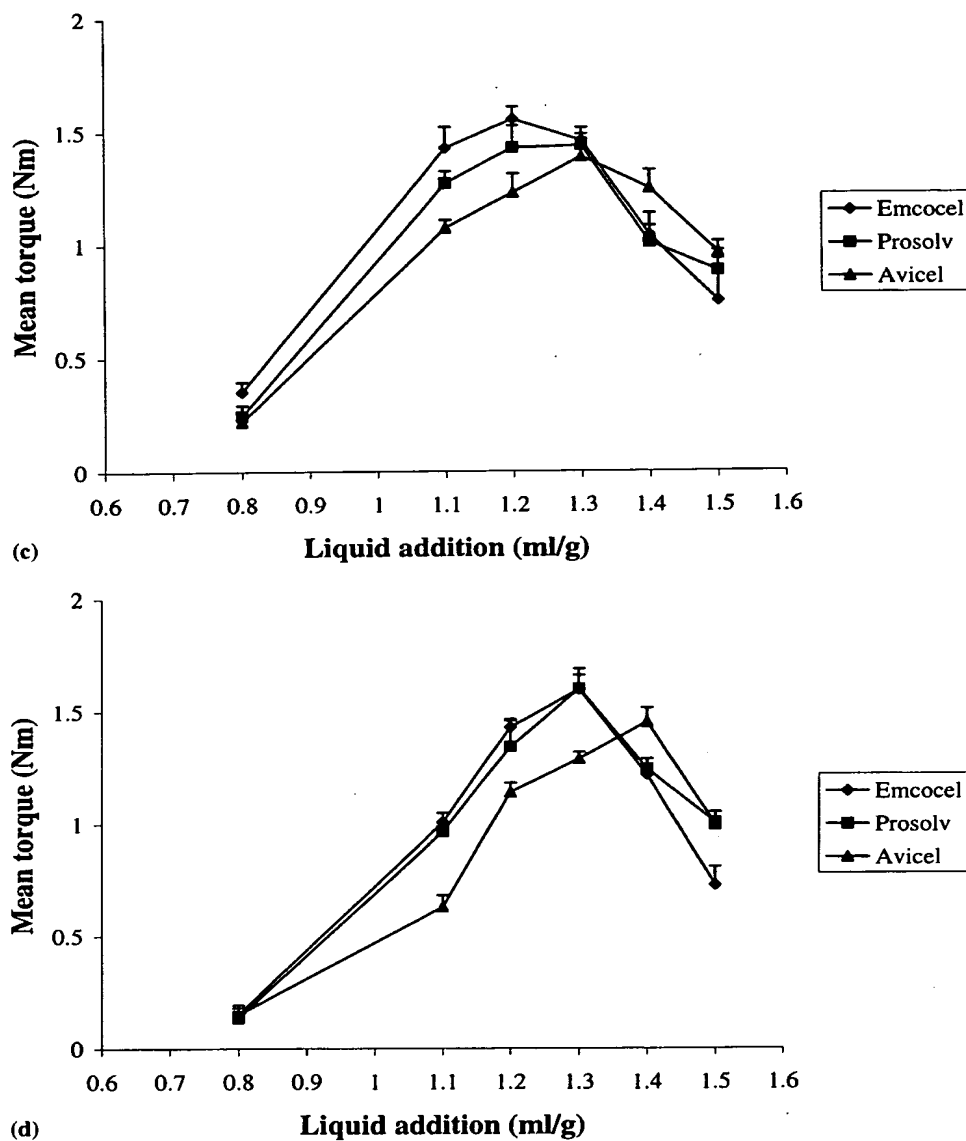


Fig. 2. (Continued)

When the wet masses achieved the peak torque (capillary state), the curves turned into ascending (Figs. 3b and 4b). With overwetted masses of MCC grades (1.5 ml g^{-1}), the torque responses achieved a plateau level after a few minutes of mixing whereas the overwetted SMCC masses did not (Fig. 5b).

Li et al. (1992) attributed water in the cellulose samples to the bulk water between fibres and to water in pore within the fibres. The amount of

water absorbed by cellulose fibres will reduce the amount of free liquid being able to form liquid bridges and will thus affect agglomerate growth by affecting the liquid saturation. Khan et al. (1988) reported that the first 3% of moisture is strongly bound into internal structure of MCC without any change in volume, but at higher water levels the particles swell increasing the particle volume. According to Davidson et al. (1994), both swelling of the cellulose fibres and increase

in the voidage of the matrix were taking place when Avicel matrices were immersed in water. Westermarck et al. (1998) found as well that with increasing moisture the size of the MCC particles increased and the voids between particles became larger. Hence, during the swelling the interparticulate voids will enlarge and the microcrystalline cellulose needs more water to fill them. Consequently, the differences both in the void volume

and in the amount of water absorbed inside the cellulose fibres are able to affect the liquid saturation.

The effect of the silicification process on the rheological profiles is shown in Fig. 2a–d. The difference between Emcocel and Prosolv mixing kinetics can be seen in the early stages of mixing (Fig. 2a). According to Alleva (1984) and Rowe and Sadeghnejad (1987) bigger torque value is

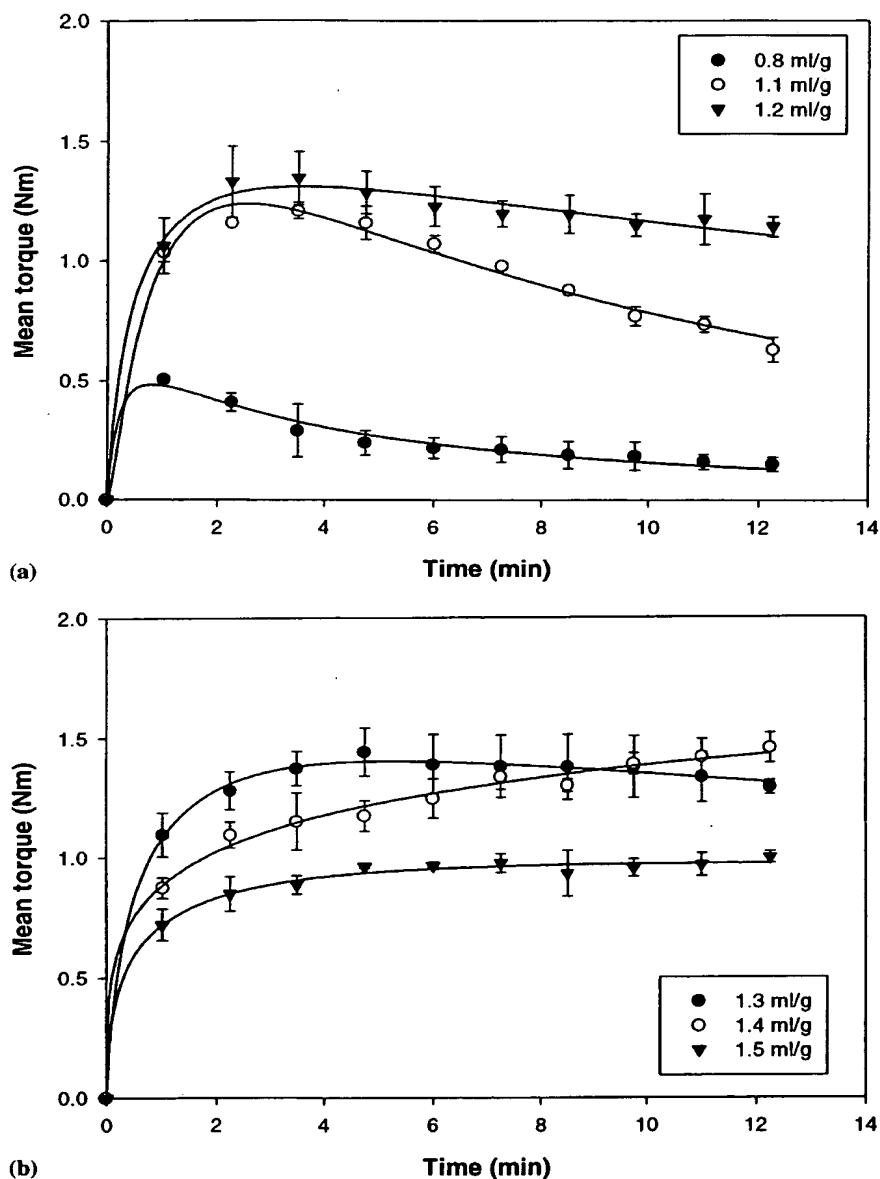


Fig. 3. Mixing kinetics of Avicel PH 101 (a) 0.8–1.2 ml g⁻¹ (b) 1.3–1.5 ml g⁻¹.

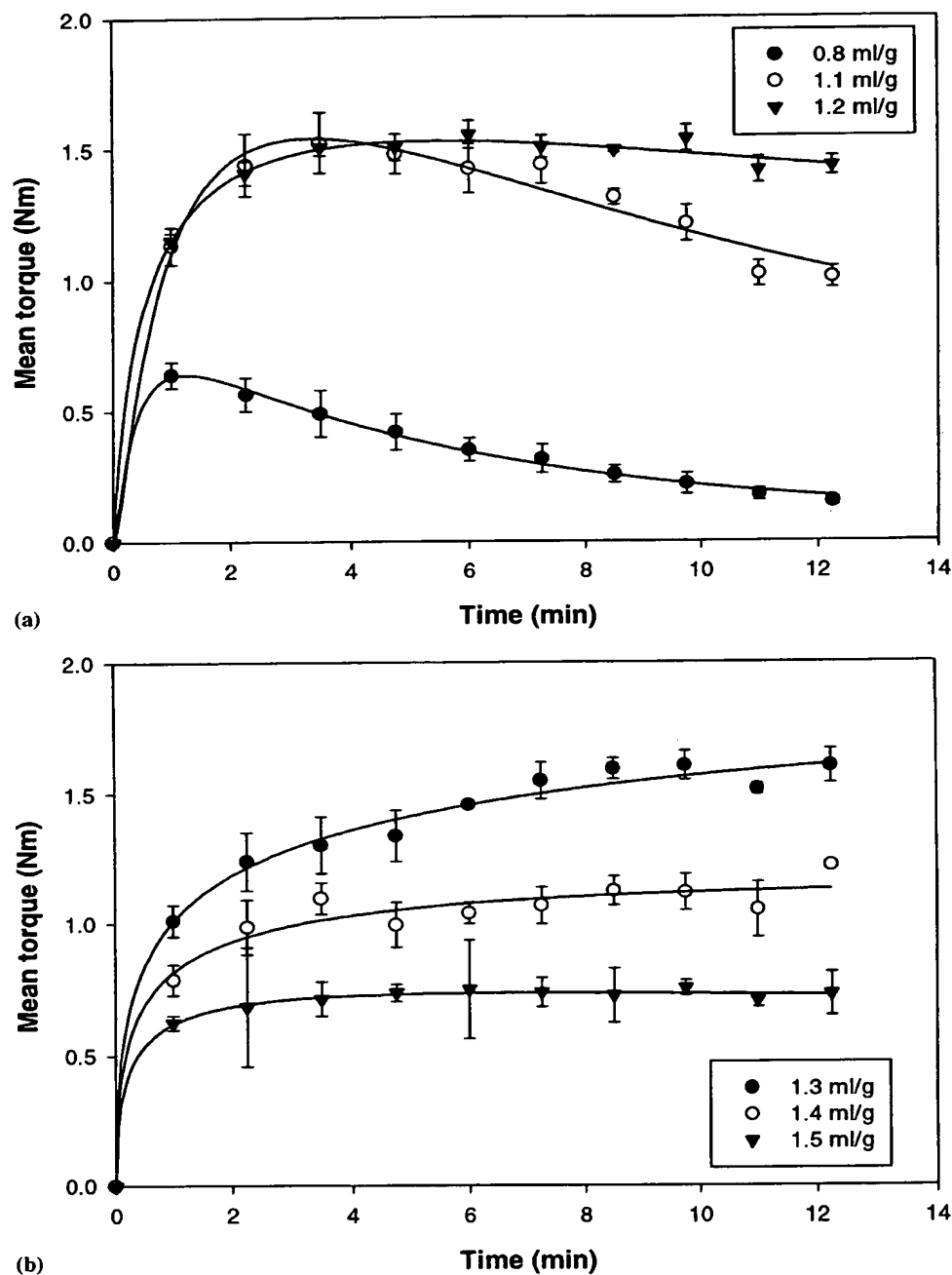


Fig. 4. Mixing kinetics of Emcocel 50 (a) 0.8–1.2 ml g⁻¹ (b) 1.3–1.5 ml g⁻¹.

consistent with the higher liquid saturation. Since the relative increase on swelling was larger for Prosolv (50.3%) than for Emcocel (45.5%), the most likely explanation for the observed differ-

ences in the mean torque is that more water is absorbed by the Prosolv causing a lower liquid saturation. After 12.25 min of mixing Emcocel and Prosolv have similar rheological profiles (Fig.

2d). This can be explained by the densification of the moist agglomerates which is said to be the most important process during granulation (Kristensen et al. 1985).

3.5.3. Effect of surface area

According to Kristensen and Schæfer (1987), the surface area of a powder material influences the amount of liquid required during wet massing,

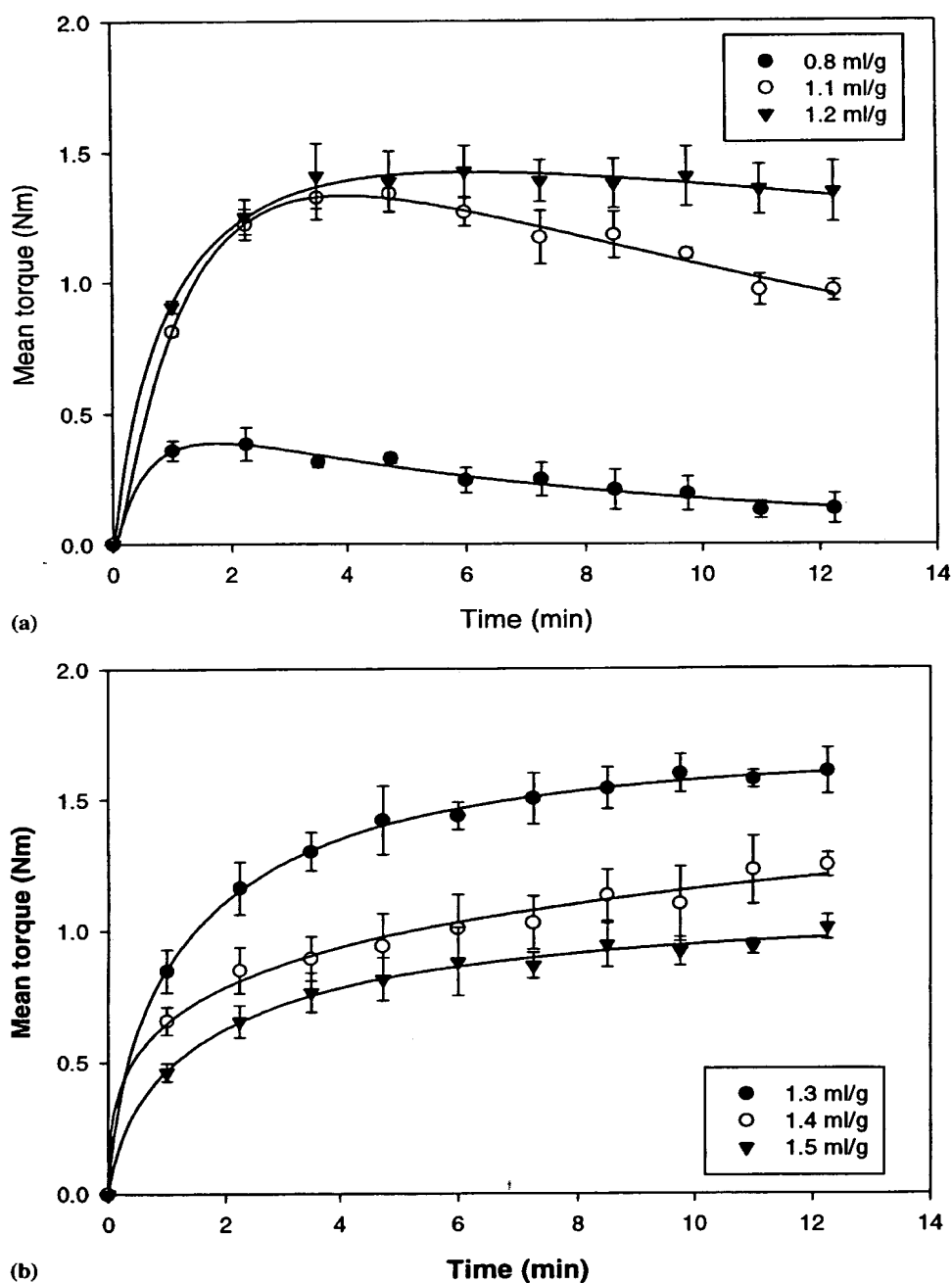


Fig. 5. Mixing kinetics of Prosolv 50 (a) 0.8–1.2 ml g⁻¹ (b) 1.3–1.5 ml g⁻¹.

since a larger surface area increases the number of liquid bridges, which can be formed between the particles. In this study, the differences in surface area were not reflected by an increase in the liquid requirement for Prosolv 50. In fact, both Prosolv 50 and Emcocel 50 achieved the maximum torque value at lower liquid level when compared with that of Avicel PH 101. Neither Hancock et al. (1992) nor Chatlapalli and Rohera (1998) could find a correlation between the critical liquid requirement and the surface area. Parker and Rowe (1991), instead, reported that the suggested relationship between liquid requirement and surface area correlated well when the cellulose particles were convoluted in shape, with numerous folds and cavities. The difference between the micromorphology of MCC and SMCC is due to the silicification which does not induce gross changes in the shape and texture of the microcrystalline cellulose particles (Tobyn et al., 1998) and, consequently, does not reflect the liquid requirement at the peak torque.

4. Conclusions

Silicified microcrystalline cellulose exhibited improved flow characteristics and increased specific surface area compared to standard microcrystalline cellulose grades. The effect of the silicification process on the rheological profiles was seen in the early stages of mixing. Since the relative increase on swelling was larger for the SMCC grade than for MCC grades, the most likely explanation for the observed differences in the mean torque is that more water is absorbed by the Prosolv causing a lower liquid saturation. After 12 min of mixing the mean torque profiles of Emcocel and Prosolv were identical whereas Avicel exhibited higher liquid content and lower torque value. Although the silicification process affected the swelling properties and, furthermore, the mixing kinetics of microcrystalline cellulose, the source of the microcrystalline cellulose had a stronger influence than silicification on the liquid requirement at peak torque.

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Characterization of microcrystalline cellulose and silicified microcrystalline cellulose wet masses using a powder rheometer

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Abstract

A powder rheometer has been used to study the properties of wet powder masses and the results have been compared to the mixer torque rheometer (MTR). Two different microcrystalline cellulose (MCC) grades (Avicel and Emcocel) and silicified microcrystalline cellulose (SMCC, Prosolv) were used as model powders. The wet massing behaviour of one material (Prosol) was studied by the powder rheometer using liquid addition experiments, while the rheological properties of wet granules were studied using both the powder rheometer and the MTR. In water addition measurements the torque behaved in a similar way to MTR measurements and the maximum value of ZTL (zero torque limit) was achieved at the capillary state of wet mass. The wet granules exhibited different behaviour in the powder rheometer and the MTR experiments, which indicates that these rheometers involve different shear forces or they measure different properties of the wet granules. Emcocel wet masses achieved the capillary state at lower liquid amount than Avicel and Prosolv masses, which indicates that Emcocel is not able to hold as much water in the internal structure as Avicel and Prosolv. The powder rheometer proved to be a sensitive piece of equipment, which can be used to study both dry and wet powder masses. It was able to distinguish wet granules from wet powder masses after liquid addition, whereas the MTR could not. However, before the powder rheometer can be properly utilised in wet powder mass studies, the problem of torque overload requires resolution. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Microcrystalline cellulose; Silicified microcrystalline cellulose; Wet powder masses; Powder rheometer; Mixer torque rheometer

1. Introduction

The interaction of microcrystalline cellulose with water is complicated and several theories have been proposed on how water is bound to cellulose (Froix and Nelson, 1975; Zografi et al., 1984; Khan and Pilpel, 1986; Fielden et al., 1988; Kleinebudde, 1997). Khan et al. (1988) reported that the first 3% of moisture is tightly bound into the internal structure of MCC without any change in volume. At higher water levels the particles swell, which causes an increase in the size of the MCC particles and the voids between particles. MCC also controls the movement of water through the wet powder mass, since it has the ability to hold large amounts of water in the internal structure (Fielden et al., 1988). MCC is an essential excipient in extrusion/spheronisation to achieve the required rheologi-

cal characteristics of the wet mass. In order to understand the behaviour of the wet powder masses in granulation and extrusion/spheronisation, it is important to study the properties of MCC in the wet state.

Alleva (1984) used a granulation rheology apparatus, and Staniforth et al. (1988) a modified shear cell to study the cohesiveness of MCC wet masses. Jerwanska et al. (1997) correlated the tensile strength of extruded cylinders to the porosity and liquid saturation of MCC wet masses. Harrison et al. (1985) used a ram extruder to screen the materials for successful extrusion/spheronisation. When a ram extruder is used as a capillary rheometer, information about the rheological properties and the elastic behaviour of wet MCC masses can be obtained (Raines et al., 1989; Chohan and Newton, 1996; Luukkonen et al., 2000a). The applicability of near infrared (NIR) spectroscopy to study SMCC and lactose wet masses was recently evaluated (Luukkonen et al., 2000b). NIR was capable of distinguishing different energetic states of water in wet powder masses. In addition, the plateau stage of SMCC water band

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heights could be correlated to the capillary state of liquid saturation.

A mixer torque rheometer (MTR) has been used to study the source variation of MCC grades (Rowe and Sadeghnejad, 1987; Parker and Rowe, 1991; Luukkonen et al., 1999a) and the mixing kinetics of water and MCC (Hancock et al., 1992; Luukkonen et al., 1999a). Recently the wet mass consistency has been used for scale-up and process control (Landín et al., 1995; Faure et al., 1999) and for evaluation of the optimum water level for extrusion/spheronisation (Souto et al., 1998; Chatlapalli and Rohera, 1998; Luukkonen et al., 1999b).

The powder rheometer is a fairly new piece of equipment, which should be able to use to study both dry and wet powder masses. Podczek (1999a,b) used this rheometer to study properties of dry MCC masses. The author found that the powder rheometer was able to identify similarities and differences in the flow, shear and packing properties of dry powders. The aim of this work was to evaluate the powder rheometer in studying MCC and SMCC wet powder masses and make comparisons with the mixer torque rheometer.

2. Materials and methods

2.1. Materials

Three different grades of microcrystalline cellulose (MCC) were studied: Avicel PH 101 manufactured by FMC (Co. Cork, Ireland) and Emcocel 50 and Prosolv 50 from Penwest Pharmaceuticals (Nastola, Finland). Prosolv 50 is silicified microcrystalline cellulose (SMCC) with a 2% (w/w) silicon dioxide concentration.

2.2. Powder rheometer measurements

2.2.1. Liquid addition

An automated powder rheometer (Wet and Dry Powder Rheometer FingerPrint, Freeman Technology, Malvern, UK) was used to study the wet massing behaviour of Prosolv 50. The equipment consists of a cylindrical measuring vessel (50×140 mm) and a rotor blade which descends into the cylinder in a helical path. The helical path is defined as the spiral movement of the impeller blade tips during downward or upward movement of the rotating impeller. A downward compaction and an upward slicing were used with the helical rotor angle of 3°. The blade tip velocity was 100 mm s⁻¹. A downward movement of the impeller is called traverse, and downward and upward movement is called cycle. Water (0.8–1.5 ml g⁻¹) was added to 35 g of dry powder during the first 6 min of mixing using a Gilson pump (Miniplus 3, Model M3 12, Villiers, France). Mixing of the wet powder mass was continued up to 15 min (30 cycles). The relationship between torque and blade height followed a semi-logarithmic

function. Experiments were performed in triplicate, and equipment-dependent software was used to derive the coefficients of the functions for each individual traverse.

2.2.2. Wet granules

The materials were mixed with six different water contents (0.8–1.5 ml g⁻¹) in a planetary mixer (Hobart, London, UK) for 10 min. The wet granules were allowed to equilibrate overnight in plastic bags before making measurements. A downward compaction and an upward slicing were used with the helical rotor angle of 3°. The blade tip velocity of 40 mm s⁻¹ was used and wet powder masses were mixed for 12.5 min (10 cycles). The wet mass column height was kept at 95–100 mm, which corresponded to 50–60 g of the wet granules depending on the moisture content. Experiments were performed in triplicate.

2.3. Mixer torque rheometer (MTR) measurements

The materials were mixed with four different water contents (1.1–1.4 ml g⁻¹) in a planetary mixer (Kenwood Chef Classic, KM 400, UK) for 10 min. The wet masses were allowed to equilibrate overnight in plastic bags before experiments. The rheological profiles of the wet powder masses were monitored using a mixer torque rheometer (Model MTR, Caleva, Dorset, UK). The rheometer was initially run empty at 52 rpm for 15 s in order to generate a baseline value. Thirty-five grams of wet powder mass was then added to the bowl, and the rheometer was run for 30 s after which data were recorded for 30 s. In order to study the effect of the mixing time, wet powder masses were mixed for a further 2.5 min. All the wet massing experiments were performed in triplicate and a mean torque value and a standard deviation were calculated.

3. Results and discussion

3.1. Liquid addition experiments

3.1.1. Mixing kinetics

The torque of Prosolv wet powder masses during liquid addition to the powder rheometer is shown as a function of blade height and mixing time in Fig. 1a–c. Provided that the powder mass is homogeneous, the torque is expected to increase as the blade height becomes lower, i.e., as the rotor approached the bottom of the vessel. Since water was added onto the top of the powder bed, water was first mixed to the upper part of the powder bed. This could be seen as a torque peak around 40 mm. The torque decreased again as the rotor approached the dry powder at the bottom of the vessel. The height of the torque peak increased with increasing water content. When mixing was continued, water was distributed further through the powder bed. This could be seen as a shift of the torque peak, especially when

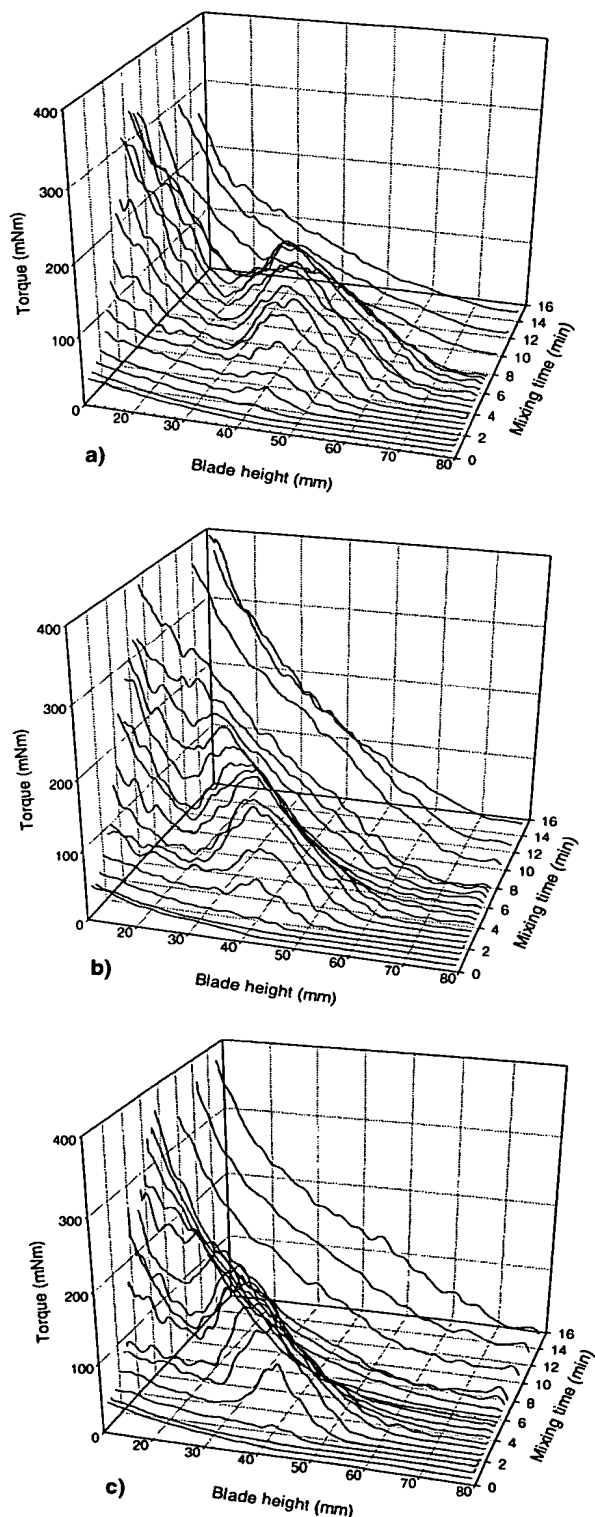


Fig. 1. Mixing kinetics of water with Prosolv in liquid addition experiments: (a) 0.8 ml g^{-1} , (b) 1.2 ml g^{-1} , (c) 1.5 ml g^{-1} .

the water content was higher. Thus it seems that water was mixed faster when the water content in the wet mass was higher. After 10 min of mixing the torque increased evenly at each water content, i.e., water was equally distributed throughout the wet powder masses.

The results are consistent with Carstensen et al. (1976), who studied the mixing kinetics of water using a planetary mixer. They found that in the initial stages part of the mixture is excessively wetted and forms large aggregates. The powder, which is not associated with these aggregates remains dry. Similarly, Alleva (1984) observed an initial force peak at low to intermediate liquid contents and attributed this to the uneven distribution of the granulating liquid and the formation of large unstable agglomerates. Thus the torque peak can be explained by the fact that water is not yet homogeneously distributed throughout the powder mass. The system exhibits an increased resistance because of increased particle size and increased autoadhesion due to the presence of excess liquid on the surface of the particles.

3.1.2. Peak torque location

To analyse down and up ward runs mathematically, Podczek (1999a) used monoexponential non-linear regression analysis to fit the data of the curves. The data analysis program of the rheometer includes only linear and logarithmic fittings to the curves, and for simplicity, the logarithmic curve fittings were used in this study. The intercept is called the zero torque limit (ZTL) as defined earlier by Podczek (1999a).

The value of ZTL is shown as a function of water content in Fig. 2a. Since water was not equally distributed before 10 min of mixing, the logarithmic curve fittings, and hence ZTL determinations could not be made with the earlier cycles. In order to demonstrate the suitability of ZTL to describe the torque behaviour of the wet powder masses, the torque values from blade height of 16 mm are shown in Fig. 2b. Fig. 2a–b are almost identical, which indicates that ZTL can also be used for wet masses. The maximum value of the ZTL was achieved at 1.2 ml g^{-1} , which thereafter decreased, as the wet mass was over-wetted. When mixing was continued for up to 15 min, the maximum value of the ZTL shifted from 1.2 to 1.3 ml g^{-1} . The results are consistent with the results obtained by mixer torque rheometry (Luukkonen et al., 1999a).

Alleva (1984) and Rowe and Sadeghnejad (1987) suggested that this behaviour is consistent with the different states of liquid saturation (pendular, funicular and capillary), as defined by Newitt and Conway-Jones (1958). With increasing liquid content the number and extent of liquid bridges increases and the funicular state is formed. A further addition of liquid fills all the inter- and intraparticle voids and pores, and the maximum (peak) torque is reached (the capillary state). Leuenberger et al. (1979) and Bier et al. (1979) found that the torque of a planetary mixer changed as the result of a change in the cohesive

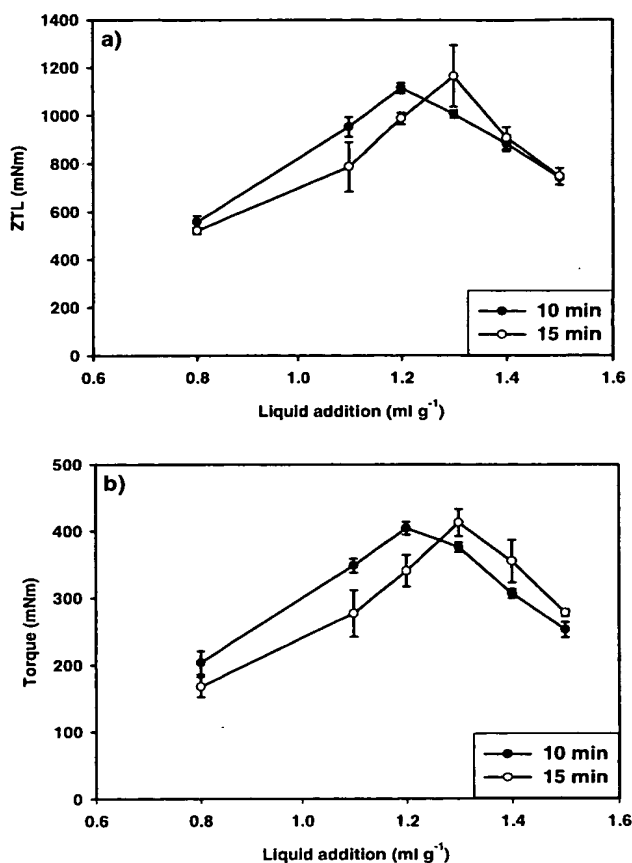


Fig. 2. Effect of mixing time (a) on the ZTL values of Prosolv (b) on the torque values of Prosolv (blade height 16 mm) in liquid addition experiments.

force or the tensile strength of the wet agglomerates. These authors were able to connect the torque curve to the liquid saturation and to the increased particle size of the wet powder mass, i.e., they were able to use torque curve to the end-point detection of the granulation process.

Liquid saturation, i.e., the degree of filling intragranular voids with binder solution depends on the amount of water and the intragranular porosity (Kristensen and Schaefer, 1987). With both methods the peak torque location shifted to higher liquid amounts as a consequence of prolonged mixing. Prolonged mixing and high shear forces are assumed to cause a densification of the mass, and this should cause the liquid saturation of about 100% at a lower liquid amount due to the reduction of interparticular voids (Kristensen and Schaefer, 1987). However, these studies were made with excipients, which do not have the same ability as MCC to swell and absorb large amounts of water to the internal structure. In the case of MCC, prolonged mixing will cause an increased absorption of water, and consequently the liquid saturation of about 100% occurs at a higher liquid amount (Luukkonen et al., 1999a).

3.2. Wet granules

3.2.1. Powder rheometer experiments

The ZTL values of wet granules for each microcrystalline cellulose grade are shown in Fig. 3a–d, with 1, 3, 9, and 19 turns of the paddle (traverses). During the first traverse Avicel and Emcocel showed very similar behaviour, whereas Prosolv had lower ZTL values. Podczek (1999a) observed that the initial traverse often differed from the following runs due to the different packing arrangement of the powder bed. After 6 min of mixing (traverse 9) Avicel and Prosolv had similar ZTL profiles, whereas the ZTL values of Emcocel were considerably higher. The biggest differences between different cellulose grades were at 1.3 and 1.4 ml g⁻¹, whereas the ZTL values were almost identical at the driest (0.8 ml g⁻¹) and the wettest (1.5 ml g⁻¹) water contents.

In general, the ZTL values of wet granules increased with increasing moisture content. The only exception to this was Emcocel, which had a peak value in ZTL at 1.4 ml g⁻¹. Consequently, the ZTL values of wet granules behaved differently than ZTL values after liquid addition to the dry powder. The torque values of wet granules were also lower than values after liquid addition. An exception to this was observed with the wet granules at the highest water content, where torque values were similar to those obtained by liquid addition. It is possible that different velocities used in liquid addition and wet granules measurements caused the observed differences between torque values. However, it has been shown previously that MCC is able to immobilize more water during granulation if high shear forces are used compared to low shear forces (Schmidt and Kleinebudde, 1998). Consequently, another explanation to different torque values could be that more water is able to go into the internal structure of microcrystalline cellulose during granulation in a planetary mixer than during water addition experiments in powder rheometer. Therefore, most of the liquid in the system is present within the granules, and not on the surface, and this causes lower interparticular contacts (lower torque values).

3.2.2. MTR experiments

The maximum consistencies (the peak torques) of the wet granules were obtained using 1.1–1.3 ml g⁻¹ of water (Fig. 4a–c). The results are consistent with Souto et al. (1998). The greatest differences between cellulose grades were seen after 0.5 mm of mixing. The differences in torque values between different cellulose grades decreased with increasing mixing time. In addition, the location of the peak torque shifted towards higher water contents. The highest torque values were obtained with Emcocel, which was the case also in the water addition experiments (Luukkonen et al., 1999a).

In MTR experiments the values of the peak torque of wet masses were attained at the same water contents both

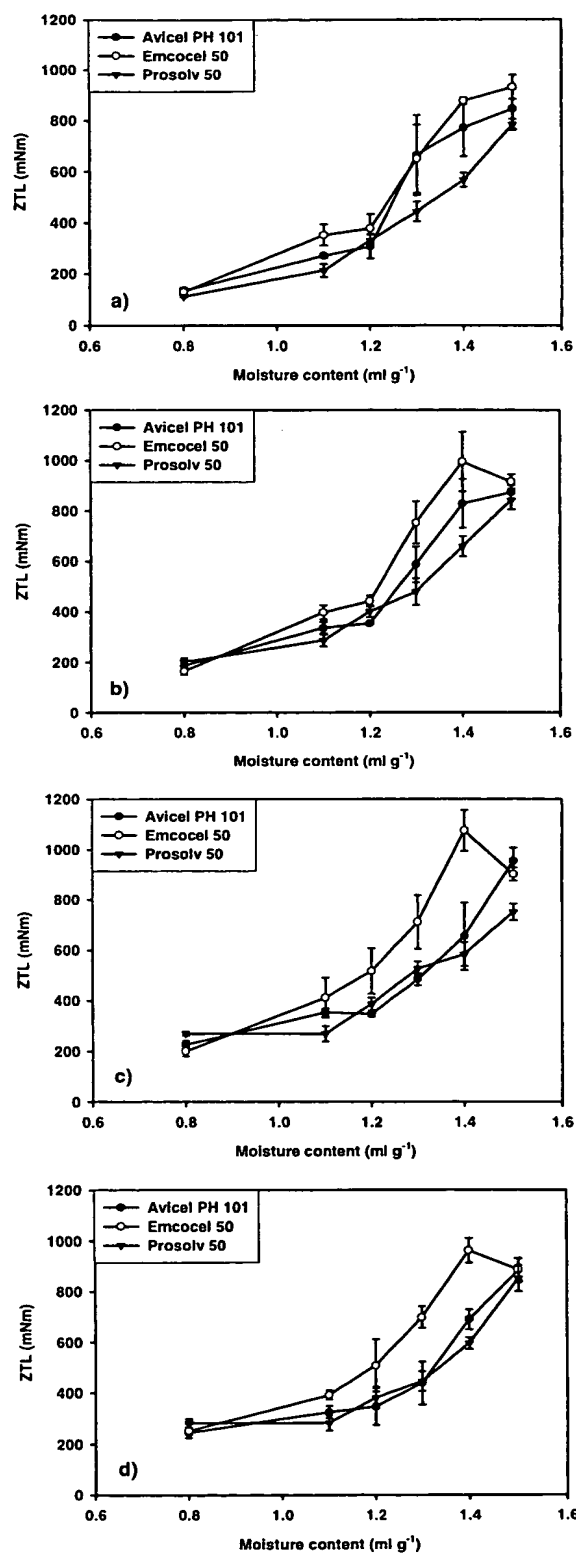


Fig. 3. Effect of mixing time on the ZTL values of wet granules: (a) traverse 1 (1.25 min), (b) traverse 3 (2.5 min), (c) traverse 9 (6.25 min), (d) traverse 19 (12.5 min).

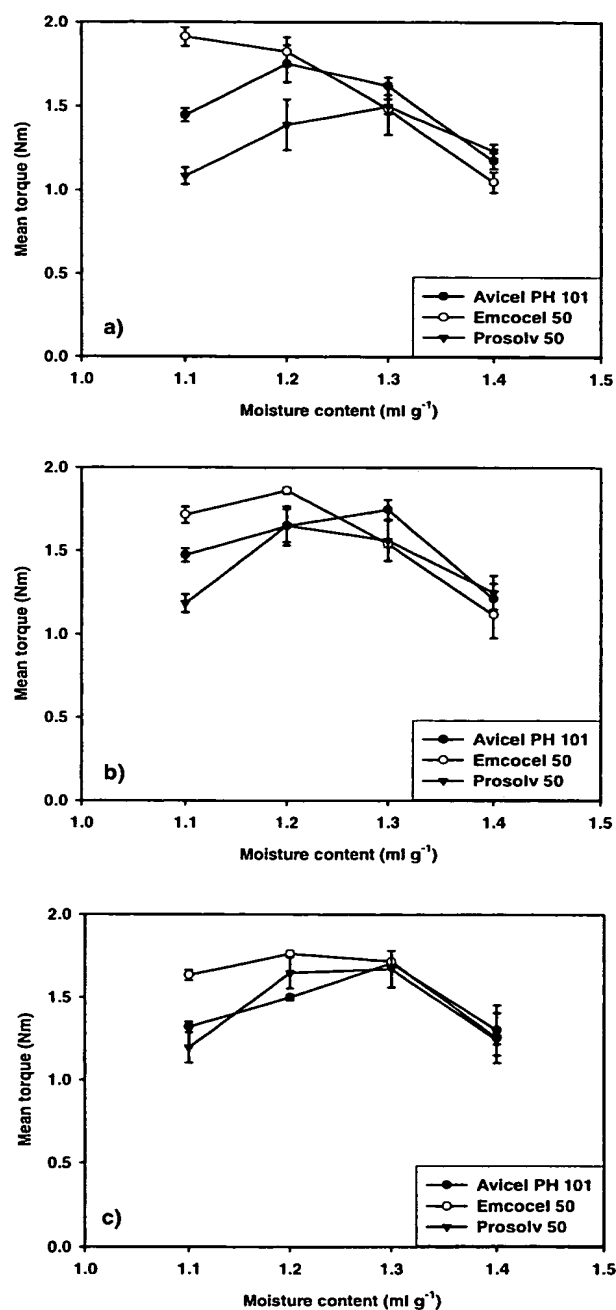


Fig. 4. Effect of mixing time on the mean torque of wet granules in MTR: (a) 0.5 min, (b) 2 min, (c) 3.25 min.

in the liquid addition and wet granule experiments. This was not the case in powder rheometer experiments. It is likely that the shear forces applied to the wet powder mass are higher in planetary mixer compared to shear forces in powder rheometer. It seems that after granulation water is more strongly bound into the internal structure of microcrystalline cellulose either because of higher shear

forces or longer equilibrium time. Consequently, more force is required to squeeze out water from MCC particles than during water addition experiment in powder rheometer.

It has been shown previously that the MTR is able to measure only the liquid saturation of the wet mass, not the standard rheological properties such as yield stress or viscosity constants (Luukkonen et al., 2000a). The wet masses containing low amounts of water exhibit low torque values, since the properties of the wet mass remain similar to those of dry material until sufficient liquid bridges are formed. The overwetted masses exhibit low torque values due to the additional water, which cannot be taken inside or between the particles, and water acts as lubricant. If the difference in the torque values between wet granules and liquid addition measurements is not caused only by different velocities, it indicates that the powder rheometer might measure also other than liquid saturation properties of the wet powder masses.

Li et al. (1992) attributed water in the cellulose samples to the bulk water between fibres and to water in pores within the fibres. The amount of water absorbed by cellulose fibres will reduce the amount of free liquid being able to form liquid bridges and will thus affect the liquid saturation. Ek and Newton (1998) associated the differences between different grades of MCC with the different interactions between the particular grade of MCC and water due to different pore structures. Emcocel wet masses exhibited the peak in the mean torque and in ZTL at a lower water content than Avicel and Prosolv masses. This indicates that Emcocel masses achieve the liquid saturation of about 100% at a lower liquid amount than Avicel and Prosolv masses, which means that Emcocel masses are not able to hold as much water in the internal structure as Avicel and Prosolv.

With the powder rheometer water addition experiments could not be done with Avicel and Emcocel, because an overload occurred at those water contents, which caused the highest measurable torque values to be exceeded. In addition, a lower blade tip velocity had to be used when wet granules were studied. These observations show the different behaviour between MCC and SMCC wet masses, which was also observed when these wet masses were studied by a capillary rheometer (Luukkonen et al., 2000a). The fact that also dry powder masses can be studied in the powder rheometer makes it more useful compared to the mixer torque rheometer.

4. Conclusions

The powder rheometer proved to be a versatile and sensitive piece of equipment, which can be used to study both dry and wet powder masses. However, before the powder rheometer can be properly utilised in wet powder mass studies, the problem of torque overload requires

resolution. In water addition experiments the torque behaved similarly to a mixer torque rheometer and the maximum torque was achieved at the capillary state of the wet mass. The wet granules exhibited different behaviour in the powder rheometer and MTR experiments, which indicates that these rheometers have different shear forces or they measure different properties of the wet granules. Emcocel wet masses achieved the capillary state at a lower liquid amount than Avicel and Prosolv masses, which indicates that Emcocel is not able to hold as much water in the internal structure as Avicel and Prosolv. If the problem of overload can be resolved, the powder rheometer will be a promising tool to characterise wet powder masses.

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Physicochemical comparison between microcrystalline cellulose and silicified microcrystalline cellulose

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Abstract

Silicified microcrystalline cellulose (SMCC) has been compared with a standard grade of microcrystalline cellulose (MCC) using several physicochemical techniques in order to elucidate any chemical or polymorphic changes in the material that could be attributed to the silicification process. Samples of SMCC, MCC and dry and wet mixes of MCC and silicon dioxide were analysed using FT-IR, ¹³C NMR, powder X-ray diffraction, mercury porosimetry, helium pycnometry and scanning electron microscopy together with particle size analysis and deaggregation studies. Analysis of the data obtained from these methods suggested that there were no discernible chemical or polymorphic differences between the samples, indicating that the 'silicification' process produces a material which is chemically and physically very similar to standard MCC. © 1998 Elsevier Science B.V. All rights reserved.

Keywords: Microcrystalline cellulose; Silicified microcrystalline cellulose

1. Introduction

Microcrystalline cellulose (MCC) is widely used as a filler and binder for wet granulation, direct compression tableting and as a filler for hard gelatin capsules. It has low chemical reactivity combined with excellent compactibility at low pressures. In a survey carried out by Shangraw

and Demarest (1993) relevant workers rated MCC the most useful filler for direct compression tableting.

However, a recent review of the direct compression properties of MCC with respect to its use as a primary excipient nevertheless pointed out a number of limitations to the use of MCC (Bolhuis and Chowhan, 1996), the most important of which were considered to be its low bulk density, high lubricant sensitivity, poor flow characteristics and the influence of moisture on the compression characteristics.

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In an attempt to reduce some of these problems some manufacturers of MCCs have introduced a number of new grades of MCC which improve some of the properties mentioned above. Most notable amongst these are high density and large particle size grades of the materials, which have been introduced by more than one company. Although these grades may have some advantages in terms of greater plasticity (Muñoz-Ruiz et al., 1994) they form weaker compacts than the base material, which may reflect a reduced surface area for bonding during compression. (Khan and Pilpel, 1986; Zeleznik et al., 1996). In addition, the reduced surface area of large particle size grades makes them more susceptible to the effects of lubricants and they can form poor ordered blends with low particle size drugs (Staniforth and Tralhao, 1996). More recently, a low bulk density grade of microcrystalline cellulose has been produced, with the aim of improving compactibility.

To address some of the functional problems outlined above it has been suggested that co-processing of MCC with other excipients may improve the performance of materials in direct compression. Included amongst these additives are starch, calcium sulphate (Bavitz and Schwartz, 1974), calcium carbonate (Mehra et al., 1987), dibasic calcium phosphate and β -cyclodextrin. However none of the co-processed materials produced by these methods has found wide commercial use or technical success although cellulose, combined with lactose (Cellactose™), is available commercially (Armstrong et al., 1996; Belda and Mielck, 1996).

Some workers have reported the beneficial properties of surface modification of MCC with silicon dioxide or silicic acid (Nürnberg and Wunderlich, 1995, 1996a,b). This process produces a material with beneficial characteristics with respect to disintegration and mechanical resistance.

A material produced by a process of 'silicification' has recently been described. Electron probe microanalysis of silicified MCC (SMCC) suggests that the process of silicification leads to the deposition of silicon, presumably in the

form of silicon dioxide, both on the outer envelope surface of the particle and on exposed surfaces within the particle (Staniforth and Tobyn, 1996). In addition, SMCC has been shown to possess a number of pharmaceutical advantages in terms of powder flow (Khalaf et al., 1997), tablet strength (Sherwood et al., 1996), lubricant sensitivity and wet granulation (Staniforth and Chatrath, 1996). Preliminary data also suggests that the material performs well in direct compression formulations (Riba et al., 1997) and roller compaction (Sheskey et al., 1997).

The aim of this study was to elucidate whether any chemical or polymorphic changes were observable in microcrystalline cellulose following the silicification process.

2. Materials and methods

2.1. Materials

Microcrystalline cellulose (Emcocel 90M™) and silicified microcrystalline cellulose (Prosolv SMCC™ 90) were obtained from Penwest Pharmaceuticals, Patterson, NY. Colloidal silica (a 15% w/w aqueous dispersion, Cab-O-Sperse, ex Cabot Corporation, USA), similar to the grade used during the silicification process, was used as a source of silicon dioxide. To prepare silicon dioxide samples a quantity of the colloidal silicon dispersion was tray-dried using a convective oven (Gallenkamp) at 60°C and milled using laboratory mill (type Glen Creston DFH 48).

2.2. Preparation of samples

Samples of MCC and SMCC 90 used throughout this study were used as received. Silicified microcrystalline cellulose SMCC 90 has a 2% w/w silicon dioxide target concentration following silicification.

A 'dry' mix consisting of 10.00 g Emcocel 90 M and 0.20 g dried silica was prepared by trituration in a mortar and pestle; a 'wet' mix was prepared by mixing 10.00 g Emcocel 90 M with

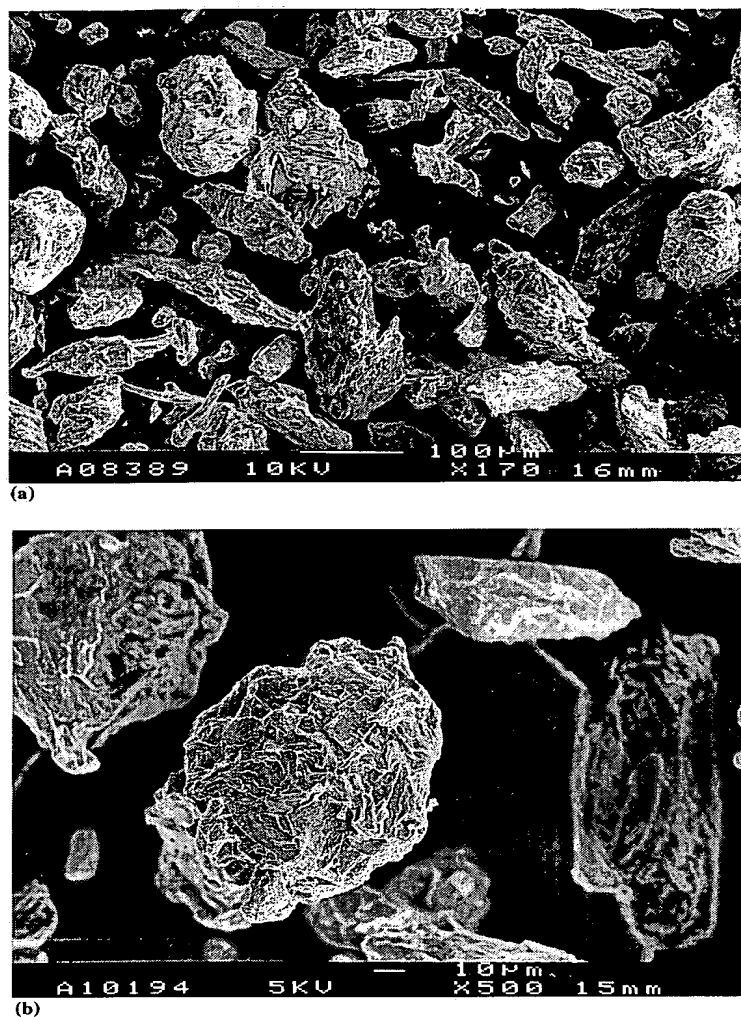


Fig. 1. SEM micrographs of MCC 90.

1.34 g colloidal silica dispersion (equivalent to 0.20 g dry solids) which had previously been diluted in 25 ml distilled water. This latter sample was also tray-dried at 60°C and milled.

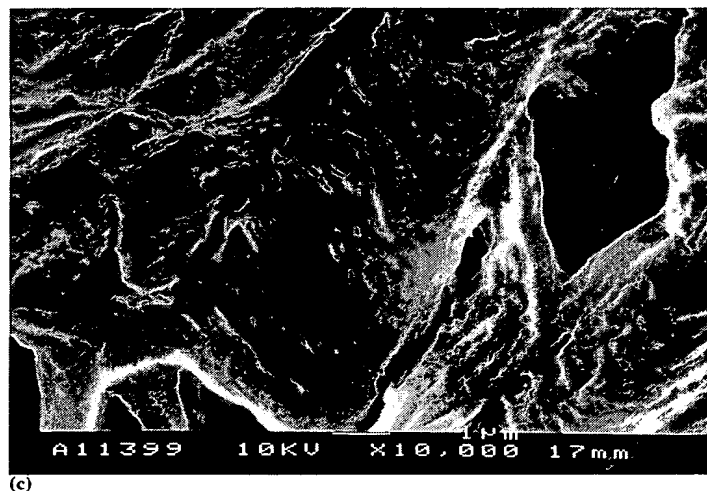
2.3. Scanning electron microscopy

Scanning electron microscopy (gold coating, Edwards Sputter Coater, UK) was performed us-

ing a Jeol 6310 (Jeol Instruments, Tokyo, Japan) system running at 5–10 KeV.

2.4. Density measurements

True density measurements for the samples were acquired using a helium pycnometer (type Accupyc 1330, Micromeritics, Dunstable, UK). Approximately 3.0 g of the sample powder was



(c)

Fig. 1. (Continued)

accurately weighed into a sample cell. The average density for each was determined from ten consecutive measurements within the cell. The results from three runs are reported.

2.5. Particle size

Representative 20 mg samples were prepared by spin riffling into a test tube followed by the removal, at random locations from the bulk of the material, using a sample thief.

Particle size data was obtained using a low-angle laser light scattering (LALLS) system (type Mastersizer X, Malvern Systems, Malvern, UK) equipped with a dry powder feeder. Three separate samples were used to determine a mean particle diameter for each material.

2.6. Deaggregation study

Aerodynamic particle diameters were determined using a laser time-of-flight system (type Aerosizer Mach 2, Amherst Process Instruments, Tewkesbury, UK). The Aerosizer was equipped with the API Aerodisperser device. Samples were analysed over a 300-s period, using a medium shear force as default. Each bulk sample was

subjected to five separate determinations, and the average aerodynamic particle diameter was calculated. 'Deagglomeration' was set to 'high', this is equivalent to a pressure drop across the orifice of 5 psi (Hindle and Byron, 1995).

2.7. Porosity measurements

Total intra-particle porosity, pore area and pore size distribution were determined using a mercury porosimeter (type Autopore II, Micromeritics, Dunstable, UK). A representative sample of 0.3–0.5 g was accurately weighed. A penetrometer was selected to ensure that 25–90% of the stem volume was employed during measurement. Mercury intrusion data was collected up to an applied pressure of 7500 psi.

2.8. Attenuated total reflectance Fourier-transform infrared spectra

The surface of each sample was characterized using attenuated total reflectance Fourier transform infrared (ATR-IR) spectroscopy. Spectra were obtained using a Nicolet Magna IR 550 Series II spectrometer (Nicolet Instruments, Warwick, UK) equipped with an ATR cell ('Golden

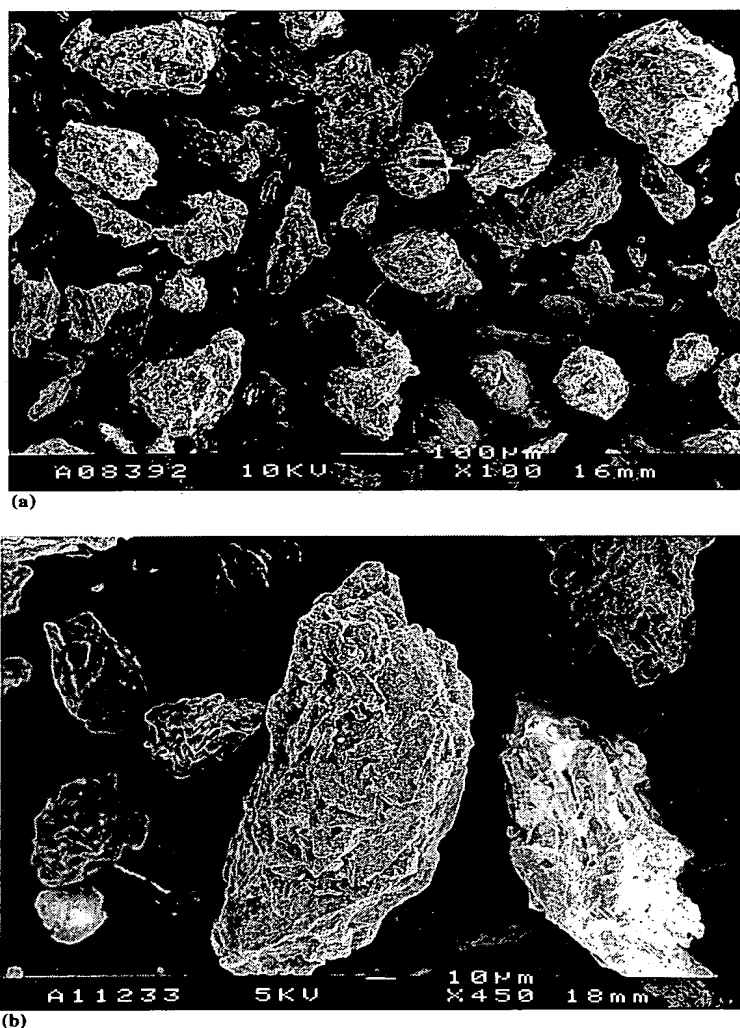


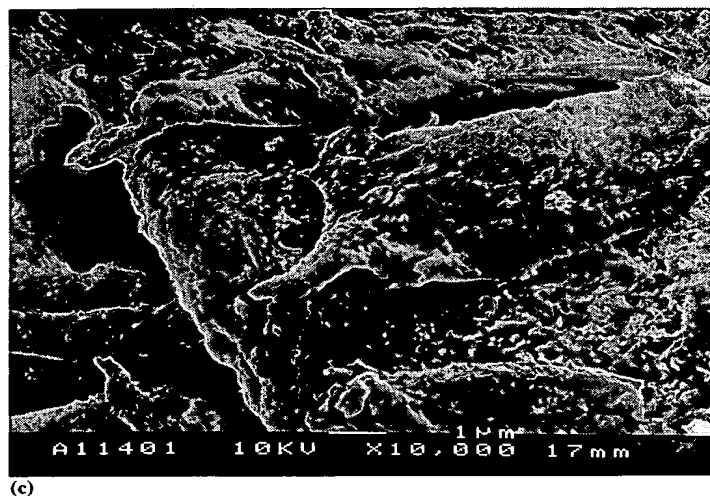
Fig. 2. SEM micrographs of SMCC 90.

Gate' model, Greaseby Specac, Orpington, Kent). Each sample was scanned 64 times at a resolution of 4 cm^{-1} between 4000 and 600 cm^{-1} .

2.9. X-ray powder diffraction studies

Diffraction patterns were obtained using an X-ray powder diffraction system (Phillips X-ray analytical, Cambridge, UK) with the following

components: 4 kW X-ray generator (a PW 1730/00); long fine-focus 2 kW copper target X-ray tube (a PW 2273/20), operated at 40 kV and 25 mA; computer-controlled vertical diffractometer goniometer (PW 1820/00); xenon proportional counter (PW 1711/10) with graphite monochromator (PW 1752/00) and automatic divergence slit assembly PW 1368/55; microprocessor diffractometer control (PW 1710/00) and diffraction



(c)

Fig. 2. (Continued)

software (PW 1877 PC-APD, version 3.5b). Each sample was analysed by a single sweep, step size 0.02° (2θ), 13s dwell time. The percentage crystallinity of powder samples was estimated from X-ray diffractograms using the technique of Nelson and O'Connor (1964).

2.10. ^{13}C nuclear magnetic resonance

The Bruker DMX-400 instrument (Bruker Instruments, Coventry, UK) was equipped with a 9.4-T magnet and 4 mm variable temperature probe. A sample (100–150 mg) was packed into a zirconia rotor with a Kel-F end cap, and spun at

the magic angle, set using kBr, of 33° with N_2 . Spin rates of 2.5–15 KHz with a sample temperature of 298 ± 2 K were used in all measurements. A single-contact cross polarisation pulse sequence was used to acquire all Magic Angle Spinning (MAS) ^{13}C spectra. High-power ^1H decoupling was used throughout. For ^{13}C - ^1H cross-polarisation experiments, a contact time of 3 ms was employed, the proton pulse width being calibrated to 3.9 ms. Pre-scan delays of 5–7 s were used and spectral widths were typically 80–140 kHz. Approximately 1024–4096 complex data points were acquired. Carbon chemical shifts were referenced to the high frequency CH_2 peak of adamantane.

Table 1
True density measurements and particle sizes of MCC samples

| Sample | Density ^a (g cm^{-3}) | Particle equivalent diameters (μm ; Malvern Mastersizer) |
|-----------------------------------|--|--|
| MCC 90 | 1.568 ± 0.003 | 122 ± 2.52 |
| SMCC 90 | 1.576 ± 0.003 | 126 ± 2.65 |
| MCC+SiO ₂ (Dry mix) | 1.576 ± 0.002 | 105 ± 2.52 |
| MCC+SiO ₂ (Wet mix) | 1.581 ± 0.001 | 146 ± 3.06 |

^a Determined by helium pycnometry.

Table 2
Aerodynamic particle size as measured by the Aerosizer
equipped with an Aerodisperser

| Sample | Vol. Average Particle Diam. (μm ; Aerosizer) |
|-----------------------------------|--|
| MCC 90 | 51.48 ± 0.62 |
| SMCC 90 | 53.83 ± 2.93 |
| MCC+SiO ₂ (Dry mix) | 31.10 ± 6.29 |
| MCC+SiO ₂ (Wet mix) | 24.02 ± 1.13 |

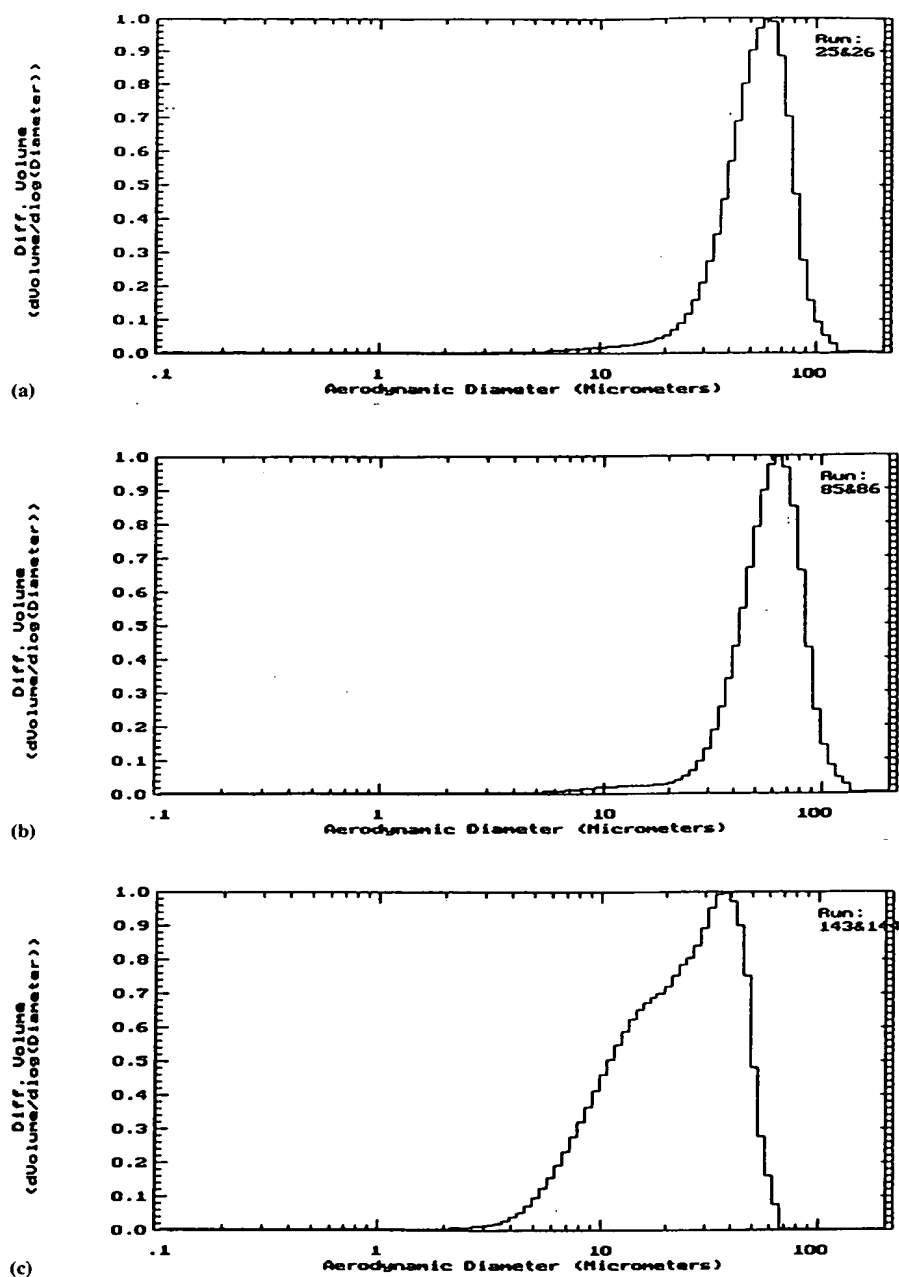


Fig. 3. Aerosizer particle size distributions of MCC (a) SMCC 90 (b) and dry mixed system (c).

Table 3
Porosity data relating to MCC samples

| Sample | Total pore area (m ² g ⁻¹) | Median pore diam. (μm) | Porosity (%) |
|--------------------------------|---|------------------------|--------------|
| MCC | 2.12 | 2.39 | 30.22 |
| SMCC 90 | 2.14 | 2.46 | 30.15 |
| MCC+SiO ₂ (Dry mix) | 2.79 | 2.60 | 34.28 |
| MCC+SiO ₂ (Wet mix) | 2.44 | 2.29 | 28.65 |

3. Results

3.1. Scanning electron microscopy

Figs. 1 and 2 show typical images of MCC and SMCC, respectively. At these resolutions no substantial morphological differences between the

two samples could be detected, although the surface of the particle in Fig. 2b does appear to contain additional features. However examination of smaller areas of specimen surfaces using high resolution, high definition scanning electron microscopy (Fig. 1c and Fig. 2c) shows distinct differences between the morphological characterisation of MCC in comparison with SMCC. Fig. 2c clearly shows an extensive surface texturisation of SMCC that we conjecture, from the dimensions and shape of these textural features, to be individual or agglomerated colloidal silica particles. Nonetheless, the fact that such textural differences are only apparent in high resolution images leads us to conclude that silicification does not induce gross changes in the shape and texture of microcrystalline cellulose particles.

3.2. Density measurements and particle size analysis

True density measurements and the average particle diameters for all the samples are displayed in Table 1.

There is little difference between the density measurements of the cellulose samples, with typical values being around 1.57 g/cm³, which is

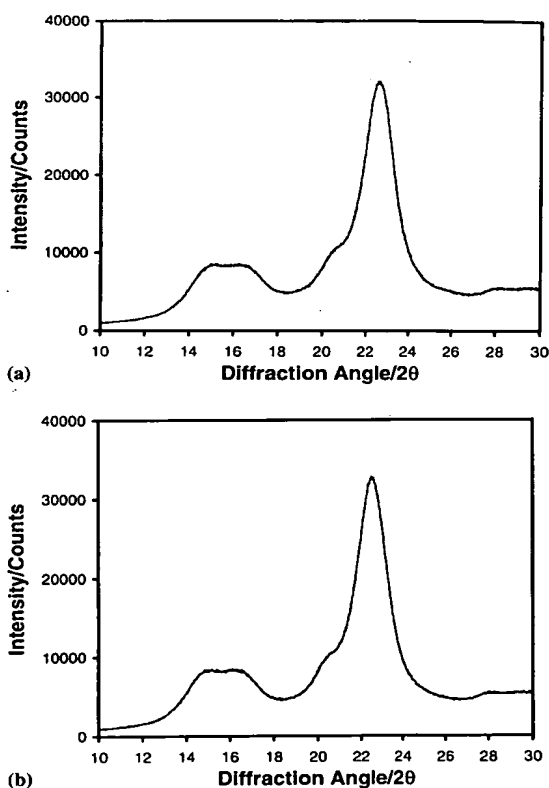


Fig. 4. X-ray diffractograms of MCC (a) and SMCC 90 (b).

Table 4
Percentage crystallinities of cellulose samples equated from X-ray diffractograms

| Sample | % Crystallinity |
|--------------------------------|-----------------|
| MCC 90 | 86 |
| SMCC 90 | 85 |
| MCC+SiO ₂ (Dry mix) | 85 |
| MCC+SiO ₂ (Wet mix) | 86 |

typical of many organic materials and is apparently minimally influenced by the presence of silicon dioxide, whether added by silicification, wet mixing or simply added by blending.

Median equivalent volume diameter determined by LALLS for SMCC was found to be comparable with regular MCC 90 M and within the normal batch to batch variation of such materials. The dry mixed sample does show a reduced particle size. This may be due to attrition during the dry mixing phase of sample manufacture. The possible contribution of deagglomeration to the apparent decrease in particle size is discussed in more detail below. Wet granulation also has an appreciable influence on the observed particle size.

3.3. Deagglomeration study

The Aerosizer, although primarily a particle size analysis equipment, has been demonstrated to be a system capable of deagglomerating particles and particle assemblies (Hindle and Byron, 1995) when used downstream of a so-called Aerodisperser device. The aerodisperser is a high-shear environment in which particles are subjected to a turbulent airstream. It is the exposure of particles to this high shear environment prior to feeding into the Aerosizer that can create some size reduction through de-agglomeration or friabilation of weaker composite materials.

Particle size data obtained using this method were found to be low (Table 2) for the grade of MCC tested, previous measurements (Table 1) and literature results normally giving values consistently above 100 μm . This discrepancy in size analysis data obtained using two different methods was considered to be a sign of the deagglomeration of primary particles of MCC, i.e. defibrillation. Electron microscopy suggests that MCC 90 grade and the equivalently sized Avicel PH102 consist of multiple fibrils each of a similar fundamental size to the 50 μm grade material. Defibrillation of MCC 90 is considered the most likely cause of the reduction in particle size found in Aerosizer analysis. However since the Aerosizer determines particle size by an aerodynamic 'time of flight' system, with particle shape influencing the observed result, this effect may be an instrument dependent phenomenon.

The results for SMCC are very similar to those obtained for the equivalent MCC grade. This was taken as an indication that the silicification process does not influence the particle shape or size, or deagglomeration characteristics of the modified material, when compared with standard grades. By contrast, for the particle size distributions for MCC simply blended with silicon dioxide (Fig. 3c) there is a noticeable downfield shoulder on the particle size distribution, one that is absent from the other two distributions.

This, once again, could be an effect due to attrition in processing. However as a substantial proportion of this shoulder is in the sub-10 μm range, this shoulder could consist of silicon dioxide. This supposition is supported by semi-quantitative X-ray energy dispersible analysis of particle surfaces (Edge et al., 1998).

3.4. Porosity measurements

The values obtained relating to the total pore areas, the median pore diameters and the porosities of the samples are shown in Table 3. These data for MCC 90 and SMCC 90 pore size characteristics were found to be very similar. The similarity in envelope surface area is a reflection of their similar particle sizes, shape and surface textures. It is interesting that there is no apparent increase in accessible surface area with the SMCC 90 sample, whereas there is with dry mixes of silicon dioxide with MCC. Previous studies have demonstrated internal deposition of silicon dioxide in silicified MCC samples (Staniforth and Tobyn, 1996).

3.5. Fourier-transform attenuated total reflectance infrared spectra

It has been demonstrated previously that ATR FT-IR is a powerful technique for the elucidation of structural change in MCC samples, with the ability to predict failure of MCC samples in compression by discovering differences not seen by other physicochemical analyses (Chatrath, 1992).

The ATR-IR spectra of the unmodified microcrystalline cellulose exhibited the following absorption bands: 2870 cm^{-1} (C–H symmetric stretching), 1595 cm^{-1} (O–H symmetric stretch-

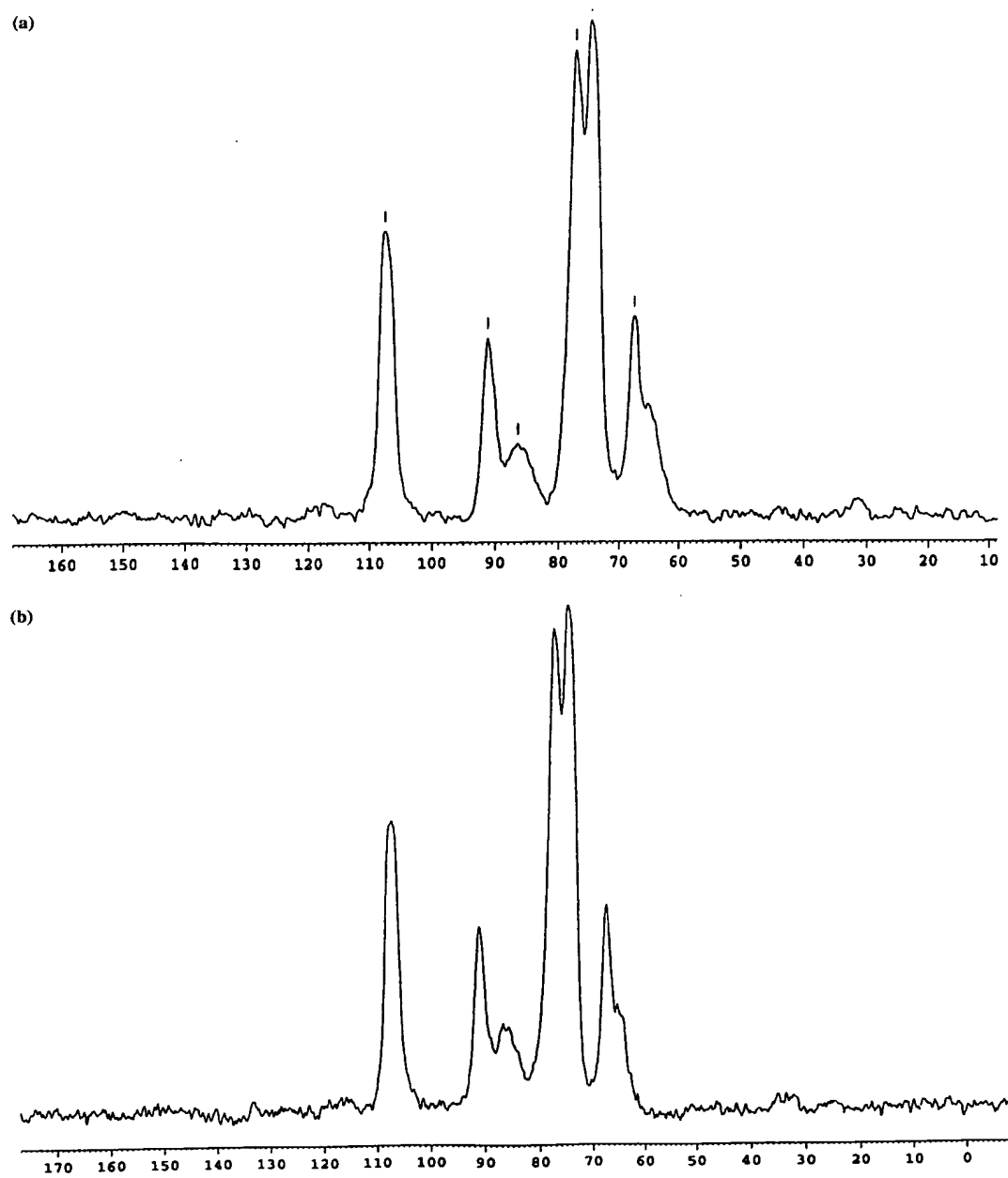


Fig. 5. Solid-state NMR spectra of MCC (a) and SMCC 90 (b).

ing), 1330 cm^{-1} (O–C–O symmetric bending) and four bands between $1200\text{--}1000\text{ cm}^{-1}$ (C–C and C–O stretching). The spectrum of silicon dioxide showed a strong band at 1070 cm^{-1} that is typical for silicon-oxygen bonds. The corresponding spectra of SMCC 90, the 'dry' mix of MCC 90 (not shown) with silica and the 'wet' mix of MCC 90 (not shown) with silica were very similar to those that obtained for the pure MCC 90. Any substantial chemical change within the cellulose structure should have resulted in shifts of the bands occurring at 2870 , 1070 and $1200\text{--}1000\text{ cm}^{-1}$ where hydrogen bonding in samples is apparent. However, no evidence of spectral difference in these regions was found with the modified samples, whether following silicification or blending. It would appear that the silicification process does not cause gross changes in the chemical bonding within the structure, and that the physical processes (dry blending and wet granulation) also appear to have little influence. The lack of substantial differences between the silicified and standard materials is further supported by subtractions of spectra, where the spectra for the modified materials were taken away from that of the base MCC material. These showed very small differences due to the physical presence of silicon dioxide, confirming its presence in the SMCC sample, but a flat baseline in all other relevant areas.

3.6. X-ray diffraction studies

Several previous studies have shown that the crystallinity of MCC samples from different commercial sources can be variable (Soltys et al., 1984; Rowe et al., 1994) and that such changes may result in different functional performance. Furthermore the presence of the polymorphic form of cellulose II in the sample can be shown to have substantial deleterious effects on the functionality of the material (Chatrath, 1992; Landin et al., 1993).

The X-ray diffractograms relating to the MCC samples are shown in Fig. 4. The percentage of crystalline material was estimated from the data according to a relationship described by Nelson and O'Connor (1964) and are shown in Table 4.

The diffractograms clearly show that the cellulose is present in the form of cellulose I and not cellulose II (shown by the absence of the doublet in the main peak intensity), and all are in contrast to the diffractogram of amorphous cellulose. There are no significant differences between any of the samples tested, once again demonstrating that there are no gross physical or chemical changes induced by silicification.

3.7. ^{13}C nuclear magnetic resonance

This technique was employed to confirm the findings from ATR-IR and X-ray diffraction as any chemical shift for a particular carbon within the cellulose is evidence of differing bond angles or differing degrees of bonding. The spectra obtained are shown in Fig. 5. In the case of MCC 90, the presence of a sharp peak at 91 ppm, corresponding to C_4 , is evidence of high degrees of crystallinity and confirm the data obtained by X-ray diffraction. The peak occurring at 67 ppm corresponds to C_6 and is indicative of the cellulose being present as cellulose I (again confirming X-ray diffraction). The shoulder associated with this peak, at 64 ppm, may be evidence of amorphous material. The ^{13}C NMR spectra for all of the samples are very similar, indicating that no substantial polymorphic or chemical changes are apparent in the modified materials.

4. Conclusion

Thus, in conclusion, it is evident from these characterisation techniques that when microcrystalline cellulose is silicified in the preparation of SMCC 90, no bulk chemical change in the MCC is observed at the resolutions tested and no observable polymorphic changes are induced.

The fundamental chemical properties of the novel material are very similar to those of the parent material. Thus the improved functionality of SMCC 90, in terms of improved bulk physical properties and mechanical characteristics, is considered to be due to some other intrinsic property rather than as a change in the base chemical parameters of the novel material.

Acknowledgements

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